WEST Search History

DATE: Thursday, March 27, 2003

Set Name side by side	Query	Hit Count	Set Name result set
DB=USPT,PGPB,JPAB,EPAB,DWPI; THES=ASSIGNEE; PLUR=YES; OP=ADJ			
L5	L4 and (mouse same secretase)	65	L5
L4	L3 and mouse	107	L4
L3	L2 and beta-secretase	150	L3
L2	L1 and amyloid precursor	309	L2
L1	secretase	432	L1

END OF SEARCH HISTORY

WEST

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Search Results - Record(s) 1 through 20 of 65 returned.

☐ 1. Document ID: US 20030059938 A1

L5: Entry 1 of 65 File: PGPB Mar 27, 2003

PGPUB-DOCUMENT-NUMBER: 20030059938
PGPUB-FILING-TYPE: new
DOCUMENT-IDENTIFIER: US 20030059938 A1

TITLE: Presenilin-deficient multipotent cell lines and screening methods for intramembrane-regulated proteolytic activities using these lines

PUBLICATION-DATE: March 27, 2003

INVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY	RULE-47
Annaert, Wim	Kontich		BE	
Strooper, Bart De	Hoeilaart		BE	
Herreman, An	Lier		BE	
Schoonjans, Luc	Wilsele		BE	
Serneels, Lutgarde	Itegem		BE	

US-CL-CURRENT: 435/354; 435/368

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | Claims | KWIC | Draw Desc | Image

☐ 2. Document ID: US 20030050302 A1

L5: Entry 2 of 65 File: PGPB Mar 13, 2003

PGPUB-DOCUMENT-NUMBER: 20030050302
PGPUB-FILING-TYPE: new
DOCUMENT-IDENTIFIER: US 20030050302 A1

TITLE: Treatment of conditions associated with amyloid processing using PKC activators

PUBLICATION-DATE: March 13, 2003

INVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY	RULE-47
Etcheberrigaray, Rene	Columbia	MD	US	
Qiao, Lixin	Arlington	VA	US	
Kozikowski, Alan P.	Princeton	NJ	US	

US-CL-CURRENT: 514/212.07

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | Claims | KWIC | Draw Desc | Image

☐ 3. Document ID: US 20030032604 A1

L5: Entry 3 of 65 File: PGPB Feb 13, 2003

PGPUB-DOCUMENT-NUMBER: 20030032604
PGPUB-FILING-TYPE: new
DOCUMENT-IDENTIFIER: US 20030032604 A1

TITLE: Smilagenin and its use

PUBLICATION-DATE: February 13, 2003

INVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY	RULE-47
Xia, Zongqin	Shanghai		CN	
Rubin, Ian	Leicester		GB	
Whittle, Brian	East Yorkshire		GB	
Gunning, Philip	Essex		GB	
Hu, Yaer	Shanghai		CN	
Brostoff, Jonathan	London		GB	
Wang, Weijun	Cambridgeshire		GB	

US-CL-CURRENT: 514/26

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | Claims | KWIC | Draw. Desc | Image

☐ 4. Document ID: US 20030022251 A1

L5: Entry 4 of 65 File: PGPB Jan 30, 2003

PGPUB-DOCUMENT-NUMBER: 20030022251
PGPUB-FILING-TYPE: new
DOCUMENT-IDENTIFIER: US 20030022251 A1

TITLE: Gamma-secretase in vitro screening assay

PUBLICATION-DATE: January 30, 2003

INVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY	RULE-47
Fuchs, Klaus	Schemmerhofen		DE	
Dorner-Ciossek, Cornelia	Ravensburg		DE	
Kostka, Marcus	Mainz		DE	
Haass, Christian	Icking		DE	
Steiner, Harald	Muenchen		DE	

US-CL-CURRENT: 435/7.21; 435/23

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | KWIC | Draw. Desc | Image

☐ 5. Document ID: US 20030022151 A1

L5: Entry 5 of 65 File: PGPB Jan 30, 2003

PGPUB-DOCUMENT-NUMBER: 20030022151
PGPUB-FILING-TYPE: new
DOCUMENT-IDENTIFIER: US 20030022151 A1

TITLE: Functional screening

PUBLICATION-DATE: January 30, 2003

INVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY	RULE-47
Thinakaran, Gopal	Chicago	IL	US	

US-CL-CURRENT: 435/4; 435/6, 435/7.2

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments KWIC | Draw Desc | Image

☐ 6. Document ID: US 20030017991 A1

L5: Entry 6 of 65 File: PGPB Jan 23, 2003

PGPUB-DOCUMENT-NUMBER: 20030017991
PGPUB-FILING-TYPE: new
DOCUMENT-IDENTIFIER: US 20030017991 A1

TITLE: Substrates and assays for beta-secretase activity

PUBLICATION-DATE: January 23, 2003

INVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY	RULE-47
Yan, Riqiang	Kalamazoo	MI	US	
Tomasselli, Alfredo G.	Kalamazoo	MI	US	
Gurney, Mark E.	Grand Rapids	MI	US	
Emmons, Thomas L.	Portage	MI	US	
Bienkowski, Michael Jerome	Portage	MI	US	
Heinrikson, Robert L.	Plainwell	MI	US	

US-CL-CURRENT: 514/18; 530/330

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments KWIC | Draw Desc | Image

☐ 7. Document ID: US 20030013881 A1

L5: Entry 7 of 65 File: PGPB Jan 16, 2003

PGPUB-DOCUMENT-NUMBER: 20030013881
PGPUB-FILING-TYPE: new
DOCUMENT-IDENTIFIER: US 20030013881 A1

TITLE: Compounds to treat Alzheimer's disease

PUBLICATION-DATE: January 16, 2003

INVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY	RULE-47
Hom, Roy	San Francisco	CA	US	
Mamo, Shumeye	Oakland	CA	US	
Tung, Jay	Belmont	CA	US	
Gailunas, Andrea	Burlingame	CA	US	
John, Varghese	San Francisco	CA	US	
Fang, Lawrence	Foster City	CA	US	

US-CL-CURRENT: 544/335; 546/176, 546/329, 548/503, 549/49, 558/418, 560/38

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments KWIC | Draw Desc | Image

☐ 8. Document ID: US 20030004147 A1

L5: Entry 8 of 65 File: PGPB Jan 2, 2003

PGPUB-DOCUMENT-NUMBER: 20030004147
PGPUB-FILING-TYPE: new
DOCUMENT-IDENTIFIER: US 20030004147 A1

TITLE: 5-beta-sapogenin and pseudosapogenin derivatives and their use in the treatment of dementia

PUBLICATION-DATE: January 2, 2003

INVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY	RULE-47
Barraclough, Paul	Maidstone		GB	
Hanson, Jim	West Sussex		GB	
Gunning, Phil	Cambs		GB	
Rees, Daryl	Sandy		GB	
Xia, Zongqin	Shanghai		CN	
Hu, Yaer	Shanghai		CN	

US-CL-CURRENT: 514/172; 514/173

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | KWIC | Draw Desc | Image

☐ 9. Document ID: US 20020194632 A1

L5: Entry 9 of 65 File: PGPB Dec 19, 2002

PGPUB-DOCUMENT-NUMBER: 20020194632
PGPUB-FILING-TYPE: new
DOCUMENT-IDENTIFIER: US 20020194632 A1

TITLE: Transgenic knockouts of BACE-1

PUBLICATION-DATE: December 19, 2002

INVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY	RULE-47
McConlogue, Lisa	Burlingame	CA	US	
Gurney, Mark E.	Reykjavik		IS	

US-CL-CURRENT: 800/12; 800/18

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | KWIC | Draw Desc | Image

☐ 10. Document ID: US 20020193317 A1

L5: Entry 10 of 65 File: PGPB Dec 19, 2002

PGPUB-DOCUMENT-NUMBER: 20020193317
PGPUB-FILING-TYPE: new
DOCUMENT-IDENTIFIER: US 20020193317 A1

TITLE: Steroidal sapogenins and their derivatives for treating alzheimer's disease

PUBLICATION-DATE: December 19, 2002

INVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY	RULE-47
Xia, Zongqin	Shanghai		CN	
Hu, Yaer	Shanghai		CN	
Rubin, Ian	Nottingham		GB	
Brostoff, Jonathan	London		GB	
Whittle, Brian	East Yorkshire		GB	
Wang, Weijun	Huntingdon		GB	
Gunning, Phil	Grantchester		GB	

US-CL-CURRENT: 514/26; 514/33

☐ 11. Document ID: US 20020183294 A1

L5: Entry 11 of 65 File: PGPB Dec 5, 2002

PGPUB-DOCUMENT-NUMBER: 20020183294
PGPUB-FILING-TYPE: new
DOCUMENT-IDENTIFIER: US 20020183294 A1

TITLE: Sapogenin derivatives and their use in the treatment of cognitive dysfunction

PUBLICATION-DATE: December 5, 2002

INVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY	RULE-47
Barraclough, Paul	Maidstone		GB	
Hanson, Jim	Steyning		GB	
Gunning, Phil	Grantchester		GB	
Rees, Daryl	Sandy		GB	
Xia, Zongqin	Shanghai		CN	
Hu, Yaer	Shanghai		CN	

US-CL-CURRENT: 514/172; 514/178

☐ 12. Document ID: US 20020164760 A1

L5: Entry 12 of 65 File: PGPB Nov 7, 2002

PGPUB-DOCUMENT-NUMBER: 20020164760
PGPUB-FILING-TYPE: new
DOCUMENT-IDENTIFIER: US 20020164760 A1

TITLE: Catalytically active recombinant memapsin and methods of use thereof

PUBLICATION-DATE: November 7, 2002

INVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY	RULE-47
Lin, Xinli	Edmond	OK	US	
Koelsch, Gerald	Oklahoma City	OK	US	
Tang, Jordan J.N.	Edmond	OK	US	

US-CL-CURRENT: 435/220; 435/252.3, 435/320.1, 435/69.1

☐ 13. Document ID: US 20020159991 A1

L5: Entry 13 of 65 File: PGPB Oct 31, 2002

PGPUB-DOCUMENT-NUMBER: 20020159991
PGPUB-FILING-TYPE: new
DOCUMENT-IDENTIFIER: US 20020159991 A1

TITLE: Modulation of Abeta levels by beta-secretase BACE2

PUBLICATION-DATE: October 31, 2002

INVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY	RULE-47
Cordell, Barbara	Palo Alto	CA	US	
Schimmoller, Frauke	Menlo Park	CA	US	
Liu, Yu-Wang	Santa Clara	CA	US	
Quon, Diana Hom	Redwood City	CA	US	

US-CL-CURRENT: 424/94.63

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments KWIC | Draw Desc | Image

☐ 14. Document ID: US 20020159947 A1

L5: Entry 14 of 65 File: PGPB Oct 31, 2002

PGPUB-DOCUMENT-NUMBER: 20020159947
PGPUB-FILING-TYPE: new
DOCUMENT-IDENTIFIER: US 20020159947 A1

TITLE: Use of small molecule radioligands to discover inhibitors of amyloid-beta peptide production and for diagnostic imaging

PUBLICATION-DATE: October 31, 2002

INVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY	RULE-47
Zaczek, Robert	Avondale	PA	US	
Olson, Richard E.	Wilmington	DE	US	
Seiffert, Dietmar A.	Boothwyn	PA	US	
Thompson, Lorin A.	Wilmington	DE	US	

US-CL-CURRENT: 424/1.49; 530/391.1

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments KWIC | Draw Desc | Image

☐ 15. Document ID: US 20020157122 A1

L5: Entry 15 of 65 File: PGPB Oct 24, 2002

PGPUB-DOCUMENT-NUMBER: 20020157122
PGPUB-FILING-TYPE: new
DOCUMENT-IDENTIFIER: US 20020157122 A1

TITLE: Beta-secretase transgenic organisms, anti-beta-secretase antibodies, and methods of use

thereof

PUBLICATION-DATE: October 24, 2002

INVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY	RULE-47
Wong, Philip C.	Timonium	MD	US	
Cai, Huaibin	Baltimore	MD	US	
Price, Donald L.	Columbia	MD	US	

US-CL-CURRENT: 800/12; 424/146.1, 435/6, 435/7.1, 435/7.2, 514/44

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | KWIC | Draw Desc | Image

☐ 16. Document ID: US 20020143177 A1

L5: Entry 16 of 65 File: PGPB Oct 3, 2002

PGPUB-DOCUMENT-NUMBER: 20020143177
PGPUB-FILING-TYPE: new
DOCUMENT-IDENTIFIER: US 20020143177 A1

TITLE: Compounds to treat alzheimer's disease

PUBLICATION-DATE: October 3, 2002

INVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY	RULE-47
Beck, James P.	Kalamazoo	MI	US	
Gailunas, Andrea	San Francisco	CA	US	
Hom, Roy	San Francisco	CA	US	
Jagodzinska, Barbara	Redwood City	CA	US	
John, Varghese	San Francisco	CA	US	
Maillard, Michel	Redwood Shores	CA	US	

US-CL-CURRENT: 544/60; 544/144, 544/238, 544/284, 544/373, 544/405, 546/148, 546/167, 548/454

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | KWIC | Draw Desc | Image

☐ 17. Document ID: US 20020128255 A1

L5: Entry 17 of 65 File: PGPB Sep 12, 2002

PGPUB-DOCUMENT-NUMBER: 20020128255
PGPUB-FILING-TYPE: new
DOCUMENT-IDENTIFIER: US 20020128255 A1

TITLE: Compounds to treat alzheimer's disease

PUBLICATION-DATE: September 12, 2002

INVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY	RULE-47
Beck, James P.	Kalamazoo	MI	US	
Fang, Lawrence Y.	Foster City	CA	US	
Freskos, John N.	Clayton	MO	US	
Gailunas, Andrea	San Francisco	CA	US	
Hom, Roy	San Francisco	CA	US	
Jagodzinska, Barbara	Redwood City	CA	US	
John, Varghese	San Francisco	CA	US	
Maillard, Michel	Redwood Shores	CA	US	
Pulley, Shon R.	Hickory Corners	MI	US	
TenBrink, Ruth E.	Kalamazoo	MI	US	

US-CL-CURRENT: 514/211.15; 514/357, 514/396, 514/423, 514/438, 514/616

☐ 18. Document ID: US 20020120947 A1

L5: Entry 18 of 65 File: PGPB Aug 29, 2002

PGPUB-DOCUMENT-NUMBER: 20020120947
PGPUB-FILING-TYPE: new
DOCUMENT-IDENTIFIER: US 20020120947 A1

TITLE: Protein-protein interactions in neurodegenerative disorders

PUBLICATION-DATE: August 29, 2002

INVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY	RULE-47
Roch, Jean-Marc	Salt Lake City	UT	US	
Bartel, Paul L.	Salt Lake City	UT	US	

US-CL-CURRENT: 800/3; 435/7.92

☐ 19. Document ID: US 20020115600 A1

L5: Entry 19 of 65 File: PGPB Aug 22, 2002

PGPUB-DOCUMENT-NUMBER: 20020115600
PGPUB-FILING-TYPE: new
DOCUMENT-IDENTIFIER: US 20020115600 A1

TITLE: Inhibitors of memapsin 2 and use thereof

PUBLICATION-DATE: August 22, 2002

INVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY	RULE-47
Koelsch, Gerald	Oklahoma City	OK	US	
Tang, Jordan J.N.	Edmond	OK	US	
Hong, Lin	Oklahoma City	OK	US	
Ghosh, Arun K.	River Forest	IL	US	

US-CL-CURRENT: 514/12; 435/184, 530/326

☐ 20. Document ID: US 20020104104 A1

L5: Entry 20 of 65 File: PGPB Aug 1, 2002

PGPUB-DOCUMENT-NUMBER: 20020104104
PGPUB-FILING-TYPE: new
DOCUMENT-IDENTIFIER: US 20020104104 A1

TITLE: METHOD FOR IDENTIFYING ALZHEIMER'S DISEASE THERAPEUTICS USING TRANSGENIC ANIMAL MODELS

PUBLICATION-DATE: August 1, 2002

INVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY	RULE-47
GAMES, KATE DORA	BELMONT	CA	US	
SCHENK, DALE BERNARD	BURLINGAME	CA	US	
MCCONLOGUE, LISA CLAIRE	SAN FRANCISCO	CA	US	
SEUBERT, PETER ANDREW	SAN FRANCISCO	CA	US	
RYDEL, RUSSELL E.	BELMONT	CA	US	

US-CL-CURRENT: 800/3; 435/29, 435/354, 800/12, 800/18

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | KWIC | Draw Desc | Image

Generate Collection Print

Terms	Documents
L4 and (mouse same secretase)	65

Display Format: - Change Format

Previous Page Next Page

WEST

Generate Collection | Print

Search Results - Record(s) 21 through 40 of 65 returned.

☐ 21. Document ID: US 20020081634 A1

L5: Entry 21 of 65 File: PGPB Jun 27, 2002

PGPUB-DOCUMENT-NUMBER: 20020081634
PGPUB-FILING-TYPE: new
DOCUMENT-IDENTIFIER: US 20020081634 A1

TITLE: Alzheimer's disease secretase, APP substrates therefor, and uses therefor

PUBLICATION-DATE: June 27, 2002

INVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY	RULE-47
Gurney, Mark E.	Reykjavik	MI	IS	
Bienkowski, Michael J.	Portage	MI	US	
Heinrikson, Robert L.	Plainwell	MI	US	
Parodi, Luis A.	Stockholm		SE	
Yan, Riqiang	Kalamazoo		US	

US-CL-CURRENT: 435/7.21; 435/226, 435/6

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | KWIC | Draw Desc | Image

☐ 22. Document ID: US 20020069424 A1

L5: Entry 22 of 65 File: PGPB Jun 6, 2002

PGPUB-DOCUMENT-NUMBER: 20020069424
PGPUB-FILING-TYPE: new
DOCUMENT-IDENTIFIER: US 20020069424 A1

TITLE: Protein-protein interactions in neurodegenerative disorders

PUBLICATION-DATE: June 6, 2002

INVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY	RULE-47
Roch, Jean-Marc	Salt Lake City	UT	US	
Bartel, Paul L.	Salt Lake City	UT	US	

US-CL-CURRENT: 800/18; 435/7.9, 800/3

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | KWIC | Draw Desc | Image

☐ 23. Document ID: US 20020064856 A1

L5: Entry 23 of 65 File: PGPB May 30, 2002

PGPUB-DOCUMENT-NUMBER: 20020064856
PGPUB-FILING-TYPE: new

DOCUMENT-IDENTIFIER: US 20020064856 A1

TITLE: Novel proteases

PUBLICATION-DATE: May 30, 2002

INVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY	RULE-47
Plowman, Gregory	San Carlos	CA	US	
Whyte, David	Belmont	CA	US	
Caenepeel, Sean	Oakland	CA	US	
Charydczak, Glen	Kentfield	CA	US	
Manning, Gerard	Menlo Park	CA	US	
Sudarsanam, Sucha	Greenbrae	CA	US	

US-CL-CURRENT: 435/226; 435/320.1, 435/325, 435/6, 435/69.1, 536/23.2

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | KWIC | Draw Desc | Image

☐ 24. Document ID: US 20020064819 A1

L5: Entry 24 of 65 File: PGPB May 30, 2002

PGPUB-DOCUMENT-NUMBER: 20020064819
PGPUB-FILING-TYPE: new
DOCUMENT-IDENTIFIER: US 20020064819 A1

TITLE: Alzheimer's disease secretase, APP substrates therefor, and uses therefor

PUBLICATION-DATE: May 30, 2002

INVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY	RULE-47
Gurney, Mark E.	Grand Rapids	MI	US	
Bienkowski, Michael J.	Portage	MI	US	
Heinrikson, Robert L.	Plainwell	MI	US	
Parodi, Luis A.	Stockholm	MI	SE	
Yan, Riqiang	Kalamazoo		US	

US-CL-CURRENT: 435/69.1; 435/320.1, 435/325, 536/23.2

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | KWIC | Draw Desc | Image

☐ 25. Document ID: US 20020059653 A1

L5: Entry 25 of 65 File: PGPB May 16, 2002

PGPUB-DOCUMENT-NUMBER: 20020059653
PGPUB-FILING-TYPE: new
DOCUMENT-IDENTIFIER: US 20020059653 A1

TITLE: Protein-protein interactions in neurodegenerative disorders

PUBLICATION-DATE: May 16, 2002

INVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY	RULE-47
Roch, Jean-Marc	Salt Lake City	UT	US	
Bartel, Paul L.	Salt Lake City	UT	US	

US-CL-CURRENT: 800/12; 424/146.1, 514/12

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | KWIC | Draw Desc | Image

☐ 26. Document ID: US 20020058276 A1

L5: Entry 26 of 65 File: PGPB May 16, 2002

PGPUB-DOCUMENT-NUMBER: 20020058276
PGPUB-FILING-TYPE: new
DOCUMENT-IDENTIFIER: US 20020058276 A1

TITLE: Proteins related to schizophrenia and uses thereof

PUBLICATION-DATE: May 16, 2002

INVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY	RULE-47
St. George-Hyslop, Peter H.	Toronto		CA	
Fraser, Paul E.	Toronto		CA	

US-CL-CURRENT: 435/6; 424/9.2, 800/3

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | KWIC | Draw Desc | Image

☐ 27. Document ID: US 20020054876 A1

L5: Entry 27 of 65 File: PGPB May 9, 2002

PGPUB-DOCUMENT-NUMBER: 20020054876
PGPUB-FILING-TYPE: new
DOCUMENT-IDENTIFIER: US 20020054876 A1

TITLE: Protein-protein interactions in neurodegenerative disorders

PUBLICATION-DATE: May 9, 2002

INVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY	RULE-47
Roch, Jean-Marc	Salt Lake City	UT	US	
Bartel, Paul L.	Salt Lake City	UT	US	

US-CL-CURRENT: 424/146.1

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | KWIC | Draw Desc | Image

☐ 28. Document ID: US 20020049988 A1

L5: Entry 28 of 65 File: PGPB Apr 25, 2002

PGPUB-DOCUMENT-NUMBER: 20020049988
PGPUB-FILING-TYPE: new
DOCUMENT-IDENTIFIER: US 20020049988 A1

TITLE: Transgenic animals harboring APP allele having swedish mutation

PUBLICATION-DATE: April 25, 2002

INVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY	RULE-47
McConlogue, Lisa	San Francisco	CA	US	
Zhao, Jun	San Diego	CA	US	
Sinha, Sukanto	San Francisco	CA	US	

US-CL-CURRENT: 800/18; 536/23.2

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | KWIC | Draw Desc | Image

☐ 29. Document ID: US 20020049303 A1

L5: Entry 29 of 65 File: PGPB Apr 25, 2002

PGPUB-DOCUMENT-NUMBER: 20020049303
PGPUB-FILING-TYPE: new
DOCUMENT-IDENTIFIER: US 20020049303 A1

TITLE: Catalytically active recombinant memapsin and methods of use thereof

PUBLICATION-DATE: April 25, 2002

INVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY	RULE-47
Tang, Jordan J. N.	Edmond	OK	US	
Lin, Xinli	Edmond	OK	US	
Koelsch, Gerald	Oklahoma City	OK	US	
Hong, Lin	Oklahoma City	OK	US	

US-CL-CURRENT: 530/350; 435/252.3, 435/320.1, 435/6, 435/69.1, 435/69.2, 530/387.9

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | KWIC | Draw Desc | Image

☐ 30. Document ID: US 20020048769 A1

L5: Entry 30 of 65 File: PGPB Apr 25, 2002

PGPUB-DOCUMENT-NUMBER: 20020048769
PGPUB-FILING-TYPE: new
DOCUMENT-IDENTIFIER: US 20020048769 A1

TITLE: Protein-protein interactions in neurodegenerative disorders

PUBLICATION-DATE: April 25, 2002

INVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY	RULE-47
Roch, Jean-Marc	Salt Lake City	UT	US	
Bartel, Paul L.	Salt Lake City	UT	US	

US-CL-CURRENT: 435/6; 435/196, 435/7.1, 530/388.1

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | KWIC | Draw Desc | Image

☐ 31. Document ID: US 20020045201 A1

L5: Entry 31 of 65 File: PGPB Apr 18, 2002

PGPUB-DOCUMENT-NUMBER: 20020045201
PGPUB-FILING-TYPE: new
DOCUMENT-IDENTIFIER: US 20020045201 A1

TITLE: Protein-protein interactions in neurodegenerative disorders

PUBLICATION-DATE: April 18, 2002

INVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY	RULE-47
Roch, Jean-Marc	Salt Lake City	UT	US	
Bartel, Paul L.	Salt Lake City	UT	US	

US-CL-CURRENT: 435/7.92

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | KWIC | Draw Desc | Image

☐ 32. Document ID: US 20020040484 A1

L5: Entry 32 of 65 File: PGPB Apr 4, 2002

PGPUB-DOCUMENT-NUMBER: 20020040484
PGPUB-FILING-TYPE: new
DOCUMENT-IDENTIFIER: US 20020040484 A1

TITLE: Protein-protein interactions in neurodegenerative disorders

PUBLICATION-DATE: April 4, 2002

INVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY	RULE-47
Roch, Jean-Marc	Salt Lake City	UT	US	
Bartel, Paul L.	Salt Lake City	UT	US	

US-CL-CURRENT: 800/8; 514/12

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | KWIC | Draw Desc | Image

☐ 33. Document ID: US 20020037315 A1

L5: Entry 33 of 65 File: PGPB Mar 28, 2002

PGPUB-DOCUMENT-NUMBER: 20020037315
PGPUB-FILING-TYPE: new
DOCUMENT-IDENTIFIER: US 20020037315 A1

TITLE: Alzheimer's disease secretase, APP substrates therefor, and uses therefor

PUBLICATION-DATE: March 28, 2002

INVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY	RULE-47
Gurney, Mark E.	Grand Rapids	MI	US	
Bienkowski, Michael J.	Portage	MI	US	
Heinrikson, Robert L.	Plainwell	MI	US	
Parodi, Luis A.	Stockholm	MI	SE	
Yan, Riqiang	Kalamazoo		US	

US-CL-CURRENT: 424/450; 424/93.21, 514/44

☐ 34. Document ID: US 20020025540 A1

L5: Entry 34 of 65 File: PGPB Feb 28, 2002

PGPUB-DOCUMENT-NUMBER: 20020025540
PGPUB-FILING-TYPE: new
DOCUMENT-IDENTIFIER: US 20020025540 A1

TITLE: Isolation of functionally active gamma- secretase protein complex and methods for detection of activity and Inhibitors thereof

PUBLICATION-DATE: February 28, 2002

INVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY	RULE-47
Roberts, Susan B.	Madison	CT	US	
Hendrick, Joseph P.	Portland	CT	US	
Vinitsky, Alexander	Stamford	CT	US	
Lewis, Martin A.	Madison	CT	US	
Smith, David W.	Madison	CT	US	
Pak, Roger Hochoon	Southington	CT	US	

US-CL-CURRENT: 435/7.9

☐ 35. Document ID: US 20020025508 A1

L5: Entry 35 of 65 File: PGPB Feb 28, 2002

PGPUB-DOCUMENT-NUMBER: 20020025508
PGPUB-FILING-TYPE: new
DOCUMENT-IDENTIFIER: US 20020025508 A1

TITLE: Process for finding a protease inhibitor

PUBLICATION-DATE: February 28, 2002

INVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY	RULE-47
Fechteler, Katja	Wiesbaden		DE	
Kostka, Marcus	Mainz		DE	
Fuchs, Klaus	Gau-Algesheim		DE	
Haass, Christian	Icking		DE	
Steiner, Harald	Muenchen		DE	

US-CL-CURRENT: 435/4; 514/1

☐ 36. Document ID: US 20020022621 A1

L5: Entry 36 of 65 File: PGPB Feb 21, 2002

PGPUB-DOCUMENT-NUMBER: 20020022621

PGPUB-FILING-TYPE: new
DOCUMENT-IDENTIFIER: US 20020022621 A1

TITLE: Benzodiazepinone beta -amyloid inhibitors: arylacetamidoalanyl derivatives

PUBLICATION-DATE: February 21, 2002

INVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY	RULE-47
Chaturvedula, Prasad V.	Cheshire	CT	US	
Yeola, Suresh	Cheshire	CT	US	
Vig, Shikha	Durham	CT	US	

US-CL-CURRENT: 514/221; 540/500

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | KWIC | Draw Desc | Image

☐ 37. Document ID: US 20020019403 A1

L5: Entry 37 of 65 File: PGPB Feb 14, 2002

PGPUB-DOCUMENT-NUMBER: 20020019403
PGPUB-FILING-TYPE: new
DOCUMENT-IDENTIFIER: US 20020019403 A1

TITLE: Methods to treat alzheimer's disease

PUBLICATION-DATE: February 14, 2002

INVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY	RULE-47
Hom, Roy	San Francisco	CA	US	
Mamo, Shumeye S.	Oakland	CA	US	
Tung, Jay	Belmont	CA	US	
Gailunas, Andrea	San Francisco	CA	US	
John, Varghese	San Francisco	CA	US	
Fang, Lawrence Y.	Foster City	CA	US	

US-CL-CURRENT: 514/256; 514/519, 514/520, 514/534

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | KWIC | Draw Desc | Image

☐ 38. Document ID: US 20020016320 A1

L5: Entry 38 of 65 File: PGPB Feb 7, 2002

PGPUB-DOCUMENT-NUMBER: 20020016320
PGPUB-FILING-TYPE: new
DOCUMENT-IDENTIFIER: US 20020016320 A1

TITLE: Compounds to treat alzheimer's disease

PUBLICATION-DATE: February 7, 2002

INVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY	RULE-47
Fang, Lawrence Y.	Foster City	CA	US	
John, Varghese	San Francisco	CA	US	

US-CL-CURRENT: 514/211.15; 514/218, 514/227.8, 514/231.5, 514/241, 514/248, 514/252.01,

514/252.13, 514/256, 514/291, 514/326, 514/422

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | KWIC | Draw Desc | Image

☐ 39. Document ID: US 20010055782 A1

L5: Entry 39 of 65 File: PGPB Dec 27, 2001

PGPUB-DOCUMENT-NUMBER: 20010055782
PGPUB-FILING-TYPE: new
DOCUMENT-IDENTIFIER: US 20010055782 A1

TITLE: Modulation of y-secretase activity

PUBLICATION-DATE: December 27, 2001

INVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY	RULE-47
Cordell, Barbara	Palo Alto	CA	US	
Higaki, Jeffrey N.	Mountain View	CA	US	
Mutz, Mitchell	Palo Alto	CA	US	

US-CL-CURRENT: 435/7.92; 435/226, 514/1

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | KWIC | Draw Desc | Image

☐ 40. Document ID: US 20010043955 A1

L5: Entry 40 of 65 File: PGPB Nov 22, 2001

PGPUB-DOCUMENT-NUMBER: 20010043955
PGPUB-FILING-TYPE: new
DOCUMENT-IDENTIFIER: US 20010043955 A1

TITLE: Smilagenin and its use

PUBLICATION-DATE: November 22, 2001

INVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY	RULE-47
Xia, Zongqin	Shanghai		CN	
Rubin, Ian	Leicester		GB	
Whittle, Brian	Hornsea		GB	
Gunning, Philip	Saffron Walden		GB	
Hu, Yaer	Shanghai		CN	
Brostoff, Jonathan	London		GB	
Wang, Weijun	Huntingdon		GB	

US-CL-CURRENT: 424/725; 424/769, 514/25

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | KWIC | Draw Desc | Image

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Terms	Documents
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Display Format: - Change Format

Previous Page Next Page

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☐ 41. Document ID: US 20010034884 A1

L5: Entry 41 of 65 File: PGPB Oct 25, 2001

PGPUB-DOCUMENT-NUMBER: 20010034884
PGPUB-FILING-TYPE: new
DOCUMENT-IDENTIFIER: US 20010034884 A1

TITLE: Abeta-peptide screening assay

PUBLICATION-DATE: October 25, 2001

INVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY	RULE-47
Peraus, Gisela	Munchen		DE	

US-CL-CURRENT: 800/3; 435/226, 435/4, 435/6

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | KWIC | Draw Desc | Image

☐ 42. Document ID: US 20010021391 A1

L5: Entry 42 of 65 File: PGPB Sep 13, 2001

PGPUB-DOCUMENT-NUMBER: 20010021391
PGPUB-FILING-TYPE: new
DOCUMENT-IDENTIFIER: US 20010021391 A1

TITLE: Alzheimer's disease secretase, APP substrates therefor, and uses therefor

PUBLICATION-DATE: September 13, 2001

INVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY	RULE-47
Gurney, Mark E.	Grand Rapids	MI	US	
Bienkowski, Michael J.	Portage	MI	US	
Heinrikson, Robert L.	Plainwell	MI	US	
Parodi, Luis A.	Stockholm	MI	SE	
Yan, Riqiang	Kalamazoo		US	

US-CL-CURRENT: 424/450; 435/226

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | KWIC | Draw Desc | Image

☐ 43. Document ID: US 20010018208 A1

L5: Entry 43 of 65 File: PGPB Aug 30, 2001

PGPUB-DOCUMENT-NUMBER: 20010018208
PGPUB-FILING-TYPE: new
DOCUMENT-IDENTIFIER: US 20010018208 A1

TITLE: Alzheimer's disease secretase, APP substrates therefor, and uses therefor

PUBLICATION-DATE: August 30, 2001

INVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY	RULE-47
Gurney, Mark E.	Grand Rapids	MI	US	
Bienkowski, Michael J.	Portage	MI	US	
Heinrikson, Robert L.	Plainwell	MI	US	
Parodi, Luis A.	Stockholm	MI	SE	
Yan, Riqiang	Kalamazoo		US	

US-CL-CURRENT: 435/325; 435/320.1, 536/23.2

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | KWIC | Draw. Desc | Image

☐ 44. Document ID: US 20010016324 A1

L5: Entry 44 of 65 File: PGPB Aug 23, 2001

PGPUB-DOCUMENT-NUMBER: 20010016324
PGPUB-FILING-TYPE: new
DOCUMENT-IDENTIFIER: US 20010016324 A1

TITLE: Alzheimer's disease secretase, APP substrates therefor, and uses therefor

PUBLICATION-DATE: August 23, 2001

INVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY	RULE-47
Gurney, Mark E.	Grand Rapids	MI	US	
Bienkowski, Michael J.	Portage	MI	US	
Heinrikson, Robert L.	Plainwell	MI	US	
Parodi, Luis A.	Stockholm	MI	SE	
Yan, Riqiang	Kalamazoo		US	

US-CL-CURRENT: 435/7.1; 435/6

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | KWIC | Draw. Desc | Image

☐ 45. Document ID: US 6509515 B2

L5: Entry 45 of 65 File: USPT Jan 21, 2003

US-PAT-NO: 6509515
DOCUMENT-IDENTIFIER: US 6509515 B2

TITLE: Transgenic mice expressing mutant human APP and forming congo red staining plaques

DATE-ISSUED: January 21, 2003

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Hsiao; Karen	North Oaks	MN		
Borchelt; David R.	Baltimore	MD		
Sisodia; Sangram S.	Baltimore	MD		

US-CL-CURRENT: 800/12; 800/18, 800/3

ABSTRACT:

Provided is a transgenic non-human eukaryotic animal whose germ cells and somatic cells contain the amyloid precursor protein sequence introduced into the animal, or an ancestor of the animal, at an embryonic stage. In mice, an age-related CNS disorder characterized by agitation, neophobia, seizures, inactivity, diminished cerebral glucose utilization, cortico-limbic gliosis, and death, develops. An acceleration of this disorder occurs in transgenic mice expressing human and mouse Alzheimer amyloid precursor proteins (APP) produced using a hamster prion protein gene-derived cosmid vector that confers position-independent, copy number-dependent expression. In transgenic mice the disorder develops in direct relationship to brain levels of transgenic APP, but mutant APP confers the phenotype at lower levels of expression than wild-type APP. The disorder occurs in the absence of extracellular amyloid deposition, indicating that some pathogenic activities of APP are dissociated from amyloid formation.

6 Claims, 41 Drawing figures
Exemplary Claim Number: 1
Number of Drawing Sheets: 22

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments KWIC | Draw Desc | Image

☐ 46. Document ID: US 6500667 B1

L5: Entry 46 of 65 File: USPT Dec 31, 2002

US-PAT-NO: 6500667
DOCUMENT-IDENTIFIER: US 6500667 B1

TITLE: Aspartyl protease 2 (Asp2) antisense oligonucleotides

DATE-ISSUED: December 31, 2002

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Gurney; Mark E.	Grand Rapids	MI		
Bienkowski; Michael J.	Portage	MI		
Heinrikson; Robert L.	Plainwell	MI		
Parodi; Luis A.	Stockholm			SE
Yan; Riqiang	Kalamazoo	MI		

US-CL-CURRENT: 435/375; 514/44, 536/23.1, 536/24.1, 536/24.5

ABSTRACT:

The present invention provides the enzyme and enzymatic procedures for cleaving the .beta. secretase cleavage site of the APP protein and associated nucleic acids, peptides, vectors, cells and cell isolates and assays. The invention further provides a modified APP protein and associated nucleic acids, peptides, vectors, cells, and cell isolates, and assays that are particularly useful for identifying candidate therapeutics for treatment or prevention of Alzheimer's disease.

8 Claims, 18 Drawing figures
Exemplary Claim Number: 1
Number of Drawing Sheets: 18

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments KWIC | Draw Desc | Image

☐ 47. Document ID: US 6440698 B1

L5: Entry 47 of 65 File: USPT Aug 27, 2002

US-PAT-NO: 6440698
DOCUMENT-IDENTIFIER: US 6440698 B1

TITLE: Alzheimer's disease secretase, APP substrates therefor, and uses therefor

DATE-ISSUED: August 27, 2002

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Gurney; Mark E.	Grand Rapids	MI	49506	
Bienkowski; Michael J.	Portage	MI	49024	
Heinrikson; Robert L.	Plainwell	MI	49080	
Parodi; Luis A.	S-11543 Stockholm			SE
Yan; Riqiang	Kalamazoo	MI	49009	

US-CL-CURRENT: 435/69.1; 435/252.3, 435/320.1, 435/325, 536/23.1

ABSTRACT:

The present invention provides the enzyme and enzymatic procedures for cleaving the .beta. secretase cleavage site of the APP protein and associated nucleic acids, peptides, vectors, cells and cell isolates and assays. The invention further provides a modified APP protein and associated nucleic acids, peptides, vectors, cells, and cell isolates, and assays that are particularly useful for identifying candidate therapeutics for treatment or prevention of Alzheimer's disease.

19 Claims, 18 Drawing figures
Exemplary Claim Number: 1
Number of Drawing Sheets: 18

☐ 48. Document ID: US 6436972 B1

L5: Entry 48 of 65 File: USPT Aug 20, 2002

US-PAT-NO: 6436972
DOCUMENT-IDENTIFIER: US 6436972 B1

TITLE: Pyridones and their use as modulators of serine hydrolase enzymes

DATE-ISSUED: August 20, 2002

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Darvesh; Sultan	Halifax			CA
Magee; David	Fredericton			CA
Valenta; Zdenek	Fredericton			CA
Martin; Earl	Halifax			CA

US-CL-CURRENT: 514/355; 514/350, 514/374, 544/100, 546/300, 546/301

ABSTRACT:

This invention relates to a compound of formula I: ##STR1##

or a pharmaceutically acceptable salt thereof; in which preferably R.sup.3, R.sup.4 and R.sup.6 are each hydrogen; X is C.dbd.O or CH.sub.2 ; and R.sup.7 and R.sup.8 are each independently selected from the group consisting of hydrogen, (C.sub.1 -C.sub.12)alkyl, (C.sub.3 -C.sub.8)cycloalkyl and (C.sub.1 -C.sub.12)alkyl(C.sub.6 -C.sub.14)aryl; or R.sup.7 and R.sup.8 when taken together form a (C.sub.2 -C.sub.7)alkylene group; or --NR.sup.7 R.sup.8 together forms a (C.sub.2 -C.sub.14)heterocyclic or substituted (C.sub.2 -C.sub.14)heterocyclic. Such

compounds modulate the activity of serine hydrolases and can be used in pharmaceutical compositions for the treatment of Alzheimer's disease.

7 Claims, 12 Drawing figures
Exemplary Claim Number: 1
Number of Drawing Sheets: 6

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | KWIC | Draw. Desc | Image

☐ 49. Document ID: US 6432944 B1

L5: Entry 49 of 65 File: USPT Aug 13, 2002

US-PAT-NO: 6432944
DOCUMENT-IDENTIFIER: US 6432944 B1

TITLE: Benzodiazepinone .beta.-amyloid inhibitors: arylacetamidoalanyl derivatives

DATE-ISSUED: August 13, 2002

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Chaturvedula; Prasad V.	Cheshire	CT		
Yeola; Suresh	Cheshire	CT		
Vig; Shikha	Durham	CT		

US-CL-CURRENT: 514/221; 540/500

ABSTRACT:

There is provided a series of arylacetamidoalanyl derivatives of benzodiazepinones of Formula I ##STR1##

wherein R.sup.1 through R.sup.7 and n are defined herein, which are inhibitors of .beta.-amyloid peptide (.beta.-AP) production and are useful in the treatment of Alzheimer's Disease and other conditions characterized by aberrant extract cellular deposition of amyloid.

9 Claims, 0 Drawing figures
Exemplary Claim Number: 1

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | KWIC | Draw. Desc | Image

☐ 50. Document ID: US 6420534 B1

L5: Entry 50 of 65 File: USPT Jul 16, 2002

US-PAT-NO: 6420534
DOCUMENT-IDENTIFIER: US 6420534 B1

TITLE: Alzheimer's disease secretase, APP substrates therefor, and uses thereof

DATE-ISSUED: July 16, 2002

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Gurney; Mark E.	Grand Rapids	MI		
Bienkowski; Michael J.	Portage	MI		
Heinrikson; Robert L.	Plainwell	MI		
Parodi; Luis A.	Stockholm			SE
Yan; Riqiang	Kalamazoo	MI		

US-CL-CURRENT: 435/226; 435/23, 435/24, 435/69.1, 530/350

ABSTRACT:

The present invention provides the enzyme and enzymatic procedures for cleaving the .beta. secretase cleavage site of the APP protein and associated nucleic acids, peptides, vectors, cells and cell isolates and assays. The invention further provides a modified APP protein and associated nucleic acids, peptides, vectors, cells, and cell isolates, and assays that are particularly useful for identifying candidate therapeutics for treatment or prevention of Alzheimer's disease.

8 Claims, 18 Drawing figures
Exemplary Claim Number: 1
Number of Drawing Sheets: 18

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | KWIC | Draw. Desc | Image

☐ 51. Document ID: US 6361975 B1

L5: Entry 51 of 65 File: USPT Mar 26, 2002

US-PAT-NO: 6361975
DOCUMENT-IDENTIFIER: US 6361975 B1

TITLE: Mouse aspartic secretase-2(mASP-2)

DATE-ISSUED: March 26, 2002

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Christie; Gary	Harlow			GB
Li; Xiaotong	Devon	PA		
Powell; David J.	Harlow			GB
Zhu; Yuan	Blue Bell	PA		

US-CL-CURRENT: 435/69.1; 435/219, 435/320.1, 435/325, 536/23.1, 536/23.2, 536/23.5

ABSTRACT:

mASP-2 polypeptides and polynucleotides and methods for producing such polypeptides by recombinant techniques are disclosed. Also disclosed are methods for screening for compounds that either agonize or antagonize mASP-2. Such compounds are expected to be useful in treatment of human diseases, including, but not limited to: Alzheimer's disease, cancer and prohormone processing.

8 Claims, 0 Drawing figures
Exemplary Claim Number: 1

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | KWIC | Draw. Desc | Image

☐ 52. Document ID: US 6358725 B1

L5: Entry 52 of 65 File: USPT Mar 19, 2002

US-PAT-NO: 6358725
DOCUMENT-IDENTIFIER: US 6358725 B1

TITLE: Mouse aspartic secretase-1 (mASP1)

DATE-ISSUED: March 19, 2002

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Christie; Gary	Harlow			GB
Li; Xiaotong	Devon	PA		
Powell; David J.	Harlow			GB
Zhu; Yuan	Blue Bell	PA		

US-CL-CURRENT: 435/212; 435/252.3, 435/320.1, 435/325, 435/354, 536/23.2

ABSTRACT:

Mouse mASP1 polypeptides and polynucleotides and method for producing such polypeptides by recombinant techniques are disclosed. Also disclosed are methods for screening for compounds that either agonize or antagonize mouse mASP1. Such compounds are expected to be useful in treatment of human diseases, including, but not limited to: Alzheimer's disease, cancer, and prohormone processing.

2 Claims, 0 Drawing figures
Exemplary Claim Number: 1

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments KWIC | Draw Desc | Image

☐ 53. Document ID: US 6333167 B1

L5: Entry 53 of 65 File: USPT Dec 25, 2001

US-PAT-NO: 6333167
DOCUMENT-IDENTIFIER: US 6333167 B1

TITLE: Methods and reagents for identifying inhibitors of proteolysis of membrane-associated proteins

DATE-ISSUED: December 25, 2001

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Quinet; Elaine M.	Princeton	NJ		
Shuey; David J.	Princeton	NJ		

US-CL-CURRENT: 435/23; 435/219, 435/254.2, 435/320.1, 435/325, 435/348, 435/349, 435/350, 435/395, 530/350, 536/23.4

ABSTRACT:

The present disclosure provides DNA constructs, genetically modified host cells and methods for identifying inhibitors of proteolysis of membrane-associated protease substrates including, but not limited to, amyloid precursor protein, a Notch protein and sterol response element binding proteins. The methods rely on chimeric proteolytic substrates containing a portion of the proteolytic substrate protein (including the proteolytic cleavage site) and a transcription repressor protein portion. Release of the repressor results in blockage of the transcription of a chimeric reporter gene which includes repressor-responsive transcription regulatory sequences and a reporter protein coding region. A specific protease inhibitor is identified by increased reporter protein activity.

48 Claims, 16 Drawing figures
Exemplary Claim Number: 1
Number of Drawing Sheets: 12

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments KWIC | Draw Desc | Image

☐ 54. Document ID: US 6313268 B1

L5: Entry 54 of 65 File: USPT Nov 6, 2001

US-PAT-NO: 6313268
DOCUMENT-IDENTIFIER: US 6313268 B1

TITLE: Secretases related to Alzheimer's dementia

DATE-ISSUED: November 6, 2001

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Hook; Vivian Y. H.	La Jolla	CA	92037	

US-CL-CURRENT: 530/350; 424/563, 424/570, 424/94.1, 424/94.2, 424/94.6, 424/94.63, 424/94.66, 435/183, 435/212, 435/226 , 530/412, 530/422, 530/427

ABSTRACT:

This invention is directed to a novel .beta.-secretase that produces the A.beta. peptide found in Alzheimer's Disease. One .beta.-secretase is a protein having a molecular weight of about 61, 81 or 88 kDa that cleaves an amyloid precursor protein (APP) substrate. Another is a protease complex having a molecular between about 180 and 200 kDa, which, in one embodiment, contains the 61, 81, and 88 kDa proteins and, in another embodiment, contains proteins having a molecular weight of about 66, 60, 33 and 29 kDa. Another .beta.-secretase has a molecular weight between about 50 and 90 kDA. The invention is also directed to methods of selecting agents that inhibit A.beta. peptide production and treating Alzheimer's disease in patients.

11 Claims, 11 Drawing figures
Exemplary Claim Number: 1
Number of Drawing Sheets: 8

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | KWIC | Draw. Desc | Image

☐ 55. Document ID: US 6291223 B1

L5: Entry 55 of 65 File: USPT Sep 18, 2001

US-PAT-NO: 6291223
DOCUMENT-IDENTIFIER: US 6291223 B1

TITLE: Mouse aspartic secretase-1 (mASP1)

DATE-ISSUED: September 18, 2001

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Christie; Gary	Harlow			GB
Li; Xiaotong	Devon	PA		
Powell; David J.	Harlow			GB
Zhu; Yuan	Blue Bell	PA		

US-CL-CURRENT: 435/212; 435/219, 435/252.3, 435/320.1, 435/325, 435/354, 536/23.2

ABSTRACT:

Mouse mASP1 polypeptides and polynucleotides and method for producing such polypeptides by recombinant techniques are disclosed. Also disclosed are methods for screening for compounds that either agonize or antagonize mouse mASP1. Such compounds are expected to be useful in treatment of human diseases, including, but not limited to: Alzheimer's disease, cancer, and prohormone processing.

8 Claims, 0 Drawing figures

Exemplary Claim Number: 1

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | KWIC | Draw Desc | Image

☐ 56. Document ID: US 6258386 B1

L5: Entry 56 of 65 File: USPT Jul 10, 2001

US-PAT-NO: 6258386
DOCUMENT-IDENTIFIER: US 6258386 B1

TITLE: Smilagenin and its use

DATE-ISSUED: July 10, 2001

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Xia; Zongqin	Shanghai			CN
Rubin; Ian	Castle Donington			GB
Whittle; Brian	Hornsea			GB
Gunning; Philip	Saffron Walden			GB
Hu; Yaer	Shanghai			CN
Brostoff; Jonathan	London			GB
Wang; Weijun	Huntingdon			GB

US-CL-CURRENT: 424/725

ABSTRACT:

The invention discloses the use of a smilagenin in the treatment of cognitive disfunction and similar conditions. Methods of treatment, and pharmaceutical compositions are also disclosed.

8 Claims, 4 Drawing figures
Exemplary Claim Number: 1
Number of Drawing Sheets: 2

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | KWIC | Draw Desc | Image

☐ 57. Document ID: US 6245964 B1

L5: Entry 57 of 65 File: USPT Jun 12, 2001

US-PAT-NO: 6245964
DOCUMENT-IDENTIFIER: US 6245964 B1

TITLE: Transgenic rodent comprising APP-Swedish

DATE-ISSUED: June 12, 2001

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
McLonlogue; Lisa C.	San Francisco	CA		
Zhao; Jun	La Jolla	CA		
Sinha; Sukanto	San Francisco	CA		

US-CL-CURRENT: 800/12; 800/14, 800/18, 800/22, 800/3

ABSTRACT:

The invention provides transgenic non-human animals and transgenic non-human mammalian cells harboring a transgene encoding an APP polypeptide comprising the Swedish mutation.

15 Claims, 6 Drawing figures
Exemplary Claim Number: 1
Number of Drawing Sheets: 5

58. Document ID: US 6245884 B1

L5: Entry 58 of 65 File: USPT Jun 12, 2001

US-PAT-NO: 6245884
DOCUMENT-IDENTIFIER: US 6245884 B1

TITLE: Secretases related to alzheimer's dementia

DATE-ISSUED: June 12, 2001

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Hook; Vivian Y. H.	La Jolla	CA	92037	

US-CL-CURRENT: 530/300; 424/9.2, 435/23, 435/29, 435/326, 435/331, 435/332, 435/69.2, 435/7.1, 530/331, 530/350, 562/545 , 562/577

ABSTRACT:

This invention provides a method of determining the proteolytic activity of the in vivo secretases, particularly the .beta.-secretase and .gamma.-secretase that produce the A.beta. peptides found in the plaques of Alzheimer Dementia (AD) patients. The invention also provides methods of isolating such secretases and methods of selecting agents that affect the activity of such secretases for developing drugs to treat or prevent dementia.

8 Claims, 5 Drawing figures
Exemplary Claim Number: 1
Number of Drawing Sheets: 5

59. Document ID: US 5976817 A

L5: Entry 59 of 65 File: USPT Nov 2, 1999

US-PAT-NO: 5976817
DOCUMENT-IDENTIFIER: US 5976817 A

TITLE: Diagnostic method for detecting Alzheimer's disease in living patients

DATE-ISSUED: November 2, 1999

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Davies-Heerema; Theresa A.	Boston	MA		
Simons; Elizabeth R.	West Newton	MA		

US-CL-CURRENT: 435/7.21; 435/7.94, 435/7.95, 436/503, 436/519, 436/811

ABSTRACT:

Upon activation, platelet .alpha.-granules' soluble contents are secreted and membrane-bound contents are translocated to the plasma membrane. Membrane-bound proteins include the .beta.-amyloid precursor protein (APP) from which the .beta.-amyloid (A.beta.) deposits found surrounding the cerebrovasculature of patients with Alzheimer's Disease (AD) may originate. It has been discovered that activated platelets from AD patients exhibit less APP processing, retain more of the protein on their surface and secrete less as soluble fragments, than do controls. There is little APP or CD62 on the surface of resting platelets, but upon activation, while control platelets exhibited more of both proteins on their surface, advanced AD patients exhibited CD62 in similar amounts to controls, but retained significantly more surface APP. AD platelets secreted similar amounts of most soluble .alpha.-granule contents as controls, but less APP fragments. These results indicate a processing defect which may be used in screening assays to help identify patients with Alzheimer's disease.

7 Claims, 12 Drawing figures
Exemplary Claim Number: 1
Number of Drawing Sheets: 5

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments KWIC | Draw. Desc | Image

☐ 60. Document ID: US 5850003 A

L5: Entry 60 of 65 File: USPT Dec 15, 1998

US-PAT-NO: 5850003
DOCUMENT-IDENTIFIER: US 5850003 A

TITLE: Transgenic rodents harboring APP allele having swedish mutation

DATE-ISSUED: December 15, 1998

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
McLonlogue; Lisa C.	San Francisco	CA		
Zhao; Jun	San Diego	CA		

US-CL-CURRENT: 800/9; 800/12, 800/14, 800/18

ABSTRACT:

The invention provides transgenic non-human animals, such as transgenic rodents and transgenic non-human mammalian cells harboring a transgene encoding an APP polypeptide comprising the Swedish mutation.

4 Claims, 6 Drawing figures
Exemplary Claim Number: 1
Number of Drawing Sheets: 5

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments KWIC | Draw. Desc | Image

Generate Collection Print

Terms	Documents
L4 and (mouse same secretase)	65

Display Format: - Change Format

WEST

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Search Results - Record(s) 61 through 65 of 65 returned.

☐ 61. Document ID: US 5777194 A

L5: Entry 61 of 65 File: USPT Jul 7, 1998

US-PAT-NO: 5777194
DOCUMENT-IDENTIFIER: US 5777194 A

TITLE: Gene-targeted mice with humanized A.beta. sequence and Swedish FAD mutation

DATE-ISSUED: July 7, 1998

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Scott; Richard W.	Wallingford	PA		
Reaume; Andrew G.	West Chester	PA		
Trusko; Stephen P.	Avondale	PA		
Siman; Robert	Wilmington	DE		

US-CL-CURRENT: 800/12; 424/9.2

ABSTRACT:

Disclosed is non-human mouse homozygous for a targeted amyloid precursor protein-encoding gene comprising: (1) a human A.beta. peptide-encoding sequence in place of the native A.beta. peptide-encoding sequence; and (2) Swedish FAD mutations.

5 Claims, 37 Drawing figures
Exemplary Claim Number: 1
Number of Drawing Sheets: 24

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | KWIC | Draw. Desc | Image

☐ 62. Document ID: US 5703129 A

L5: Entry 62 of 65 File: USPT Dec 30, 1997

US-PAT-NO: 5703129
DOCUMENT-IDENTIFIER: US 5703129 A

TITLE: 5-amino-6-cyclohexyl-4-hydroxy-hexanamide derivatives as inhibitors of .beta.-amyloid protein production

DATE-ISSUED: December 30, 1997

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Felsenstein; Kevin	Madison	CT		
Smith; David W.	Madison	CT		
Poss; Michael A.	Lawrenceville	NJ		
Chaturvedula; Prasad	Cheshire	CT		
Sloan; Charles P.	Wallingford	CT		

US-CL-CURRENT: 514/613; 514/620, 514/623, 564/156, 564/188, 564/191

ABSTRACT:

A series of 5-amino-6-cyclohexyl-4-hydroxy-hexanamide derivatives of Formula I have been synthesized. ##STR1## As inhibitors of the production of .beta.-amyloid protein from .beta.-amyloid precursor protein, these compounds are expected to be effective in treating patients suffering from or susceptible to conditions or disorders linked to brain accumulation of .beta.-amyloid protein; e.g., Alzheimer's Disease and Down's Syndrome.

9 Claims, 0 Drawing figures
Exemplary Claim Number: 1,7

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments KWIC | Draw. Desc | Image

☐ 63. Document ID: US 5612486 A

L5: Entry 63 of 65 File: USPT Mar 18, 1997

US-PAT-NO: 5612486
DOCUMENT-IDENTIFIER: US 5612486 A

TITLE: Transgenic animals harboring APP allele having swedish mutation

DATE-ISSUED: March 18, 1997

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
McConlogue; Lisa C.	San Francisco	CA		
Zhao; Jun	San Diego	CA		

US-CL-CURRENT: 800/12; 536/23.1, 536/23.5, 800/18

ABSTRACT:

The invention provides transgenic non-human animals and transgenic non-human mammalian cells harboring a transgene encoding an APP polypeptide comprising the Swedish mutation.

4 Claims, 4 Drawing figures
Exemplary Claim Number: 1
Number of Drawing Sheets: 4

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments KWIC | Draw. Desc | Image

☐ 64. Document ID: US 5604102 A

L5: Entry 64 of 65 File: USPT Feb 18, 1997

US-PAT-NO: 5604102
DOCUMENT-IDENTIFIER: US 5604102 A

TITLE: Methods of screening for .beta.-amyloid peptide production inhibitors

DATE-ISSUED: February 18, 1997

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
McConlogue; Lisa C.	San Francisco	CA		
Schenk; Dale B.	Pacifica	CA		
Seubert; Peter A.	South San Francisco	CA		
Sinha; Sukanto	San Francisco	CA		
Zhao; Jun	La Jolla	CA		

US-CL-CURRENT: 435/7.1; 424/9.2, 435/7.21, 530/350

ABSTRACT:

Processing of .beta.-amyloid precursor protein (.beta.APP) is monitored by detecting the secretion of a soluble amino-terminal fragment or .beta.APP (ATF-.beta.APP) resulting from cleavage of .beta.APP at the amino-terminus of .beta.-amyloid peptide. Secretion of ATF-.beta.APP in animal models may be monitored to identify inhibitors of .beta.-amyloid production. The ATF-.beta.APP may be detected using antibodies and other specific binding substances which recognize a carboxy terminal residue on the fragment. Animals expressing the Swedish mutation of .beta.APP are described which produce abundant amounts of ATF-.beta.APP.

19 Claims, 13 Drawing figures
Exemplary Claim Number: 1
Number of Drawing Sheets: 8

☐ 65. Document ID: MX 2001008063 A1 WO 200047618 A2 AU 200040009 A EP 1165609 A2 GB 2364059 A

L5: Entry 65 of 65 File: DWPI Dec 1, 2001

DERWENT-ACC-NO: 2000-533011
DERWENT-WEEK: 200282
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TITLE: Purified beta-secretase protein used in assays to discover inhibitors which can be used for the treatment of amyloidogenic diseases e.g. Alzheimer's disease

INVENTOR: ANDERSON, J P; BASI, G ; DOANE, M T ; FRIGON, N ; JOHN, V ; MCCONLOGUE, L ; POWER, M ; SINHA, S ; TATSUNO, G ; TUNG, J ; WANG, S

PRIORITY-DATA: 1999US-139172P (June 15, 1999), 1999US-119571P (February 10, 1999)

PATENT-FAMILY:

PUB-NO	PUB-DATE	LANGUAGE	PAGES	MAIN-IPC
MX 2001008063 A1	December 1, 2001		000	A01K067/027
WO 200047618 A2	August 17, 2000	E	141	C07K014/47
AU 200040009 A	August 29, 2000		000	C07K014/47
EP 1165609 A2	January 2, 2002	E	000	C07K014/47
GB 2364059 A	January 16, 2002		000	C07K014/47

INT-CL (IPC): A01 K 67/027; A61 K 38/08; A61 P 25/28; C07 K 7/06; C07 K 14/47; C07 K 16/40; C12 N 1/19; C12 N 1/21; C12 N 5/16; C12 N 9/64; C12 N 15/57; C12 Q 1/68; G01 N 33/50

ABSTRACTED-PUB-NO: WO 200047618A
BASIC-ABSTRACT:

NOVELTY - A beta -secretase enzyme protein (I) purified to apparent homogeneity, is new.

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for the following:

(1) a crystalline protein composition (II) formed from a purified beta -secretase protein;

(2) an isolated protein (III) comprising a polypeptide that:

(a) is fewer than 450 amino acids (aa) long;

(b) includes an aa sequence at least 90% identical to (xiv) including conservative substitutions; and

(c) exhibits beta -secretase activity shown by the ability to cleave a substrate which is the 695 aa isotype of beta -amyloid precursor protein (beta -APP) between aa 596 and 597, MBP-C125wt or MBP-C125sw;

(3) a composition comprising (III) and a beta -secretase substrate or inhibitor molecule;

(4) an isolated mouse beta -secretase protein enzyme with aa sequence (x) given in the specification;

(5) an antibody which binds specifically to a purified beta -secretase protein comprising a polypeptide that includes an aa sequence at least 90% identical to (xiv) including conservative substitutions and lacking significant immunoreactivity with a protein comprising sequence (i) or (vii);

(6) an isolated nucleic acid (IV) comprising a sequence of nucleotides that encodes a beta -secretase protein at least 95% identical to a protein that has aa sequence (ii), (iii), (iv), (v), (vi), (vii), (viii), (ix), (xi), (xii), (xiii), (xiv) or (xv) or a complementary sequence to any of these nucleic acid sequences but specifically excluding a nucleic acid encoding a protein with sequence (i);

(7) an expression vector comprising (IV) operably linked to regulatory sequences effective for expression of (IV) in the host cell;

(8) a heterologous cell transfected with the vector of (7) which expresses a biologically active beta -secretase;

(9) a heterologous cell (V) comprising a nucleic acid molecule encoding (III) and a nucleic acid encoding a beta -secretase substrate molecule which are both linked to regulatory molecules which control their expression;

(10) a method of screening for compounds which inhibit beta -amyloid peptide (A beta) production comprising contacting (III) with a test compound and a beta -secretase substrate and selecting the test compound capable of inhibiting A beta production if the beta -secretase polypeptide exhibits less activity in the presence of the compound than in the absence of the compound;

(11) a method of screening for compounds which inhibit A beta production comprising measuring binding of (I) or (III) with a beta -secretase inhibitor compound in the presence of the test compound and selecting the test compound as a beta -secretase active site binding compound if binding of the inhibitor in the presence of the test compound is less than the binding of the inhibitor in the absence of the test compound;

(12) a beta -secretase inhibitor compound (VI) selected by the method of (11) or (12);

(13) a beta -secretase inhibitor comprising a peptide containing sequence VM(X)VAEF, EVMXVAEF or (P10-P4'staD-->V);

(14) a screening kit comprising (I) or (III), a cleavable beta -secretase substrate and a device for detecting cleavage of the substrate by beta -secretase;

(15) a knock-out mouse characterized by inactivation or deletion of an endogenous beta -secretase gene;

(16) a method of treating a patient afflicted with or having a predilection for Alzheimer's disease or other cerebrovascular amyloidosis comprising blocking the enzymatic hydrolysis of APP to A beta in the patient by administering a compound to inhibit (III);

(17) a method of inhibiting enzymatic proteolysis of APP to A beta in a tissue comprising contacting a tissue with a compound to inhibit activity of (III);

(18) a composition for treatment of Alzheimer's disease or other cerebrovascular amyloidosis characterized by deposition of A beta peptide, where the active compound of the composition inhibits the enzymatic activity of (III);

(19) a method for diagnosing the presence or a predilection for Alzheimer's disease in a patient by detecting the expression level of a gene comprising a nucleic acid encoding beta -secretase in a cell sample from a patient and if the expression level is greater than a predetermined control expression level diagnosing the condition; and

(20) a method of purifying a beta -secretase protein enzyme molecule comprising contacting an impure sample containing beta -secretase enzyme activity with an affinity matrix that includes a beta -secretase inhibitor.

X = hydroxyethylene or statine.

The beta -secretase protein has a sequence (i) of 501 aa. The peptides are derived from (i); (ii) comprises residues 63-452, (iii) comprises residues 63-501, (iv) comprises residues 58-501, (v) comprises residues 58-452, (vi) comprises residues 22-452, (vii) comprises residues 46-452, (viii) comprises residues 46-501, (ix) comprises residues 22-501, (xi) comprises residues 1-419, (xii) comprises residues 1-452, (xiii) comprises residues 1-420, (xiv) comprises residues 63-423 and (xv) comprises residues 46-419 of (i).

ACTIVITY - Nootropic; neuroprotectve.

No biological data is given.

MECHANISM OF ACTION - beta -secretase inhibitor.

USE - Inhibitors of beta -secretase discovered by the detection method are administered to a mammalian subject e.g. mouse carrying a transgene encoding human beta -APP, with Alzheimer's disease or Alzheimer's disease-like pathology to test if they maintain or improve cognitive ability or reduce the plaque burden (claimed). The compounds are used for the treatment of amyloidogenic diseases e.g. Alzheimer's disease.

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=> s .beta.-secretase
L1          239 FILE MEDLINE
L2          438 FILE CAPLUS
L3          390 FILE SCISEARCH
L4          149 FILE LIFESCI
L5          457 FILE BIOSIS
L6          342 FILE EMBASE

TOTAL FOR ALL FILES
L7         2015 .BETA.-SECRETASE

=> s l7 and (purif? or character? or isolat?)


TOTAL FOR ALL FILES
L14         591 L7 AND (PURIF? OR CHARACTER? OR ISOLAT?)

=> s L14 not 2000-2003/py
TOTAL FOR ALL FILES
L21         170 L14 NOT 2000-2003/PY

=> dup rem l21
PROCESSING COMPLETED FOR L21
L22          48 DUP REM L21 (122 DUPLICATES REMOVED)

=> d ibib abs 1-48

L22  ANSWER 1 OF 48  BIOSIS  COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER:    1999:508117  BIOSIS
DOCUMENT NUMBER:     PREV199900508117
TITLE:               Enzymes point way to potential Alzheimer's therapies.
AUTHOR(S):           Pennisi...
SOURCE:              Science (Washington D C), (Oct. 22, 1999) Vol. 286, No.
                     5440, pp. 650-651.
                     ISSN: 0036-8075.
DOCUMENT TYPE:       News Announcement
LANGUAGE:            English
AB   In a discovery with therapeutic potential for Alzheimer's disease,
     scientists at Amgen Inc. have reported the isolation of a
     beta-secretase, an enzyme involved in the production of
     beta-amyloid.

L22  ANSWER 2 OF 48     MEDLINE                          DUPLICATE 1
ACCESSION NUMBER:    2000036510     MEDLINE
DOCUMENT NUMBER:     20036510   PubMed ID: 10567340
TITLE:               Generation of the amyloid-beta peptide N terminus in
                     Saccharomyces cerevisiae expressing human Alzheimer's
                     amyloid-beta precursor protein.
AUTHOR:              Greenfield J P; Xu H; Greengard P; Gandy S; Seeger M
CORPORATE SOURCE:    Laboratory of Molecular Neuroscience, Fisher Center for
                     Research on Alzheimer Disease, The Rockefeller University,
                     New York, New York 10021, USA.
CONTRACT NUMBER:     AG09464 (NIA)
     AG10491 (NIA)
SOURCE:              JOURNAL OF BIOLOGICAL CHEMISTRY, (1999 Nov 26) 274 (48)
                     33843-6.
                     Journal code: 2985121R. ISSN: 0021-9258.
PUB. COUNTRY:        United States
DOCUMENT TYPE:       Journal; Article; (JOURNAL ARTICLE)
LANGUAGE:            English
FILE SEGMENT:        Priority Journals
ENTRY MONTH:         199912
ENTRY DATE:          Entered STN: 20000113
                     Last Updated on STN: 20000113
                     Entered Medline: 19991229
AB   The Alzheimer's amyloid-beta precursor protein (betaAPP) is a type 1
     membrane-spanning protein from which the Alzheimer's disease amyloid-beta
     peptide (Abeta) is proteolytically derived. To date, attempts to identify
     the enzymes responsible for Abeta generation have failed. Here we report
     the accumulation of Abeta-immunoreactive peptides in yeast expressing
```

human betaAPP. **Characterization** of these peptides by metabolic labeling, immunoprecipitation with Abeta-specific antibodies, and N-terminal radiosequencing indicates that these peptides include the Abeta peptide at their N termini. The Abeta-like peptides generated in yeast were recovered predominantly as 8- and 12-14-kDa species. A 4-kDa species was recovered either when a protease-deficient strain was used to prevent breakdown or when the 8- and 12-14-kDa species were treated with disaggregating agents. The likely existence in yeast of enzymes generating the Abeta N terminus indicates that the molecular identification of yeast **beta-secretase**-like enzymes may be accomplished using genetic screens or empirical approaches based upon the sequenced genome of Saccharomyces cerevisiae.

L22 ANSWER 3 OF 48 MEDLINE DUPLICATE 2
ACCESSION NUMBER: 1999223517 MEDLINE
DOCUMENT NUMBER: 99223517 PubMed ID: 10207012
TITLE: gamma-Secretase, evidence for multiple proteolytic activities and influence of membrane positioning of substrate on generation of amyloid beta peptides of varying length.
AUTHOR: Murphy M P; Hickman L J; Eckman C B; Uljon S N; Wang R; Golde T E
CORPORATE SOURCE: Department of Pharmacology, Mayo Clinic Jacksonville, Jacksonville, Florida 32224, USA.
CONTRACT NUMBER: AG-16065 (NIA)
SOURCE: JOURNAL OF BIOLOGICAL CHEMISTRY, (1999 Apr 23) 274 (17) 11914-23.
Journal code: 2985121R. ISSN: 0021-9258.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199905
ENTRY DATE: Entered STN: 19990601
Last Updated on STN: 20000303
Entered Medline: 19990520

AB gamma-Secretase activity is the final cleavage event that releases the amyloid beta peptide (Abeta) from the **beta-secretase** cleaved carboxyl-terminal fragment of the amyloid beta protein precursor (APP). No protease responsible for this highly unusual, purportedly intramembranous, cleavage has been definitively identified. We examined the substrate specificity of gamma-secretase by mutating various residues within or adjacent to the transmembrane domain of the APP and then analyzing Abeta production from cells transfected with these mutant APPs by enzyme-linked immunosorbent assay and mass spectrometry. Abeta production was also analyzed from a subset of transmembrane domain APP mutants that showed dramatic shifts in gamma-secretase cleavage in the presence or absence of pepstatin, an inhibitor of gamma-secretase activity. These studies demonstrate that gamma-secretase's cleavage specificity is primarily determined by location of the gamma-secretase cleavage site of APP with respect to the membrane, and that gamma-secretase activity is due to the action of multiple proteases exhibiting both a pepstatin- sensitive activity and a pepstatin-insensitive activity. Given that gamma-secretase is a major therapeutic target in Alzheimer's disease these studies provide important information with respect to the mechanism of Abeta production that will direct efforts to **isolate** the gamma-secretases and potentially to develop effective therapeutic inhibitors of pathologically relevant gamma-secretase activities.

L22 ANSWER 4 OF 48 MEDLINE
ACCESSION NUMBER: 1999432177 MEDLINE
DOCUMENT NUMBER: 99432177 PubMed ID: 10500121
TITLE: Cellular mechanisms of beta-amyloid production and secretion.
AUTHOR: Sinha S; Lieberburg I
CORPORATE SOURCE: Elan Pharmaceuticals, South San Francisco, CA 94080, USA.. ssinha@elanpharma.com
SOURCE: PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA, (1999 Sep 28) 96 (20) 11049-53.
Ref: 46

Journal code: 7505876. ISSN: 0027-8424.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199910
ENTRY DATE: Entered STN: 19991101
Last Updated on STN: 20000303
Entered Medline: 19991021

AB The major constituent of senile plaques in Alzheimer's disease is a 42-aa peptide, referred to as beta-amyloid (Abeta). Abeta is generated from a family of differentially spliced, type-1 transmembrane domain (TM)-containing proteins, called APP, by endoproteolytic processing. The major, relatively ubiquitous pathway of APP metabolism in cell culture involves cleavage by alpha-secretase, which cleaves within the Abeta sequence, thus precluding Abeta formation and deposition. An alternate secretory pathway, enriched in neurons and brain, leads to cleavage of APP at the N terminus of the Abeta peptide by **beta-secretase** , thus generating a cell-associated beta-C-terminal fragment (beta-CTF). A pathogenic mutation at codons 670/671 in APP (APP "Swedish") leads to enhanced cleavage at the **beta-secretase** scissile bond and increased Abeta formation. An inhibitor of vacuolar ATPases, bafilomycin, selectively inhibits the action of **beta-secretase** in cell culture, suggesting a requirement for an acidic intracellular compartment for effective **beta-secretase** cleavage of APP. beta-CTF is cleaved in the TM domain by gamma-secretase(s), generating both Abeta 1-40 (90%) and Abeta 1-42 (10%). Pathogenic mutations in APP at codon 717 (APP "London") lead to an increased proportion of Abeta 1-42 being produced and secreted. Missense mutations in PS-1, localized to chromosome 14, are pathogenic in the majority of familial Alzheimer's pedigrees. These mutations also lead to increased production of Abeta 1-42 over Abeta 1-40. Knockout of PS-1 in transgenic animals leads to significant inhibition of production of both Abeta 1-40 and Abeta 1-42 in primary cultures, indicating that PS-1 expression is important for gamma-secretase cleavages. Peptide aldehyde inhibitors that block Abeta production by inhibiting gamma-secretase cleavage of beta-CTF have been discovered.

L22 ANSWER 5 OF 48 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 1999:255949 BIOSIS
DOCUMENT NUMBER: PREV199900255949
TITLE: Peptidomimetic probes and molecular modeling suggest that Alzheimer's gamma-secretase is an intramembrane-cleaving aspartyl protease.
AUTHOR(S): Wolfe, Michael S. (1); Xia, Weiming; Moore, Chad L.; Leatherwood, Dartha D.; Ostaszewski, Beth; Rahmati, Talat; Donkor, Isaac O.; Selkoe, Dennis J.
CORPORATE SOURCE: (1) Department of Pharmaceutical Sciences, University of Tennessee, Memphis, TN, 38163 USA
SOURCE: Biochemistry, (April 13, 1999) Vol. 38, No. 15, pp. 4720-4727.
ISSN: 0006-2960.
DOCUMENT TYPE: Article
LANGUAGE: English
SUMMARY LANGUAGE: English

AB The amyloid beta-protein (Abeta), implicated in the pathogenesis of Alzheimer's disease (AD), is a proteolytic metabolite generated by the sequential action of beta- and gamma-secretases on the amyloid precursor protein (APP). The two main forms of Abeta are 40- and 42-amino acid C-terminal variants, Abeta40 and Abeta42. We recently described a difluoro ketone peptidomimetic (1) that blocks Abeta production at the gamma-secretase level (Wolfe, M. S., et al. (1998) J. Med. Chem. 41, 6-9). Although designed to inhibit Abeta42 production, 1 also effectively blocked Abeta40 formation. Various amino acid changes in 1 still resulted in inhibition of Abeta40 and Abeta42 production, suggesting relatively loose sequence specificity by gamma-secretase. The alcohol counterparts of selected difluoro ketones also lowered Abeta levels, indicating that the ketone carbonyl is not essential for activity and suggesting that these compounds inhibit an aspartyl protease. Selected compounds inhibited the

aspartyl protease cathepsin D but not the cysteine protease calpain, corroborating previous suggestions that gamma-secretase is an aspartyl protease with some properties similar to those of cathepsin D. Also, since the gamma-secretase cleavage sites on APP are within the transmembrane region, we consider the hypothesis that this region binds to gamma-secretase as an alpha-helix and discuss the implications of this model for the mechanism of certain forms of hereditary AD.

L22 ANSWER 6 OF 48 MEDLINE DUPLICATE 3
ACCESSION NUMBER: 1999155098 MEDLINE
DOCUMENT NUMBER: 99155098 PubMed ID: 10037494
TITLE: cDNA cloning and molecular **characterization** of human brain metalloprotease MP100: a **beta-secretase** candidate?.
AUTHOR: Huber G; Thompson A; Gruninger F; Mechler H; Hochstrasser R; Hauri H P; Malherbe P
CORPORATE SOURCE: Pharma Division, Preclinical CNS Research, F. Hoffmann-La Roche Ltd., Basel, Switzerland.
SOURCE: JOURNAL OF NEUROCHEMISTRY, (1999 Mar) 72 (3) 1215-23. Journal code: 2985190R. ISSN: 0022-3042.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199903
ENTRY DATE: Entered STN: 19990326
Last Updated on STN: 20000303
Entered Medline: 19990318
AB Metalloprotease MP100 was originally **isolated** as a **beta-secretase** candidate from human brain using a beta-amyloid precursor protein (beta-APP)-derived p-nitroanilide (pNA) peptide substrate. Peptide sequences from **purified** MP100 were now found to resemble sequences reported for a puromycin-sensitive aminopeptidase (PSA) highly enriched in brain, and cDNA cloning revealed nearly complete homology of MP100 to PSA, with only a single bp difference resulting in an amino acid change at position 184. Another MP100 cDNA encoded a protein with a 36-amino acid deletion (positions 180-217) and a two-amino acid insertion after Val533. **Purified** recombinant human MP100 cleaved the original pNA substrate as well as a free beta-site-spanning amyloid beta (A beta) peptide (A beta(-10/+10)), generating A beta(1-10). The latter substrate, however, remained uncleaved, if N- and C-terminally blocked, and also **purified** beta-APP was not cleaved. Double immunoimaging revealed partial, patchy, colocalization of beta-APP and MP100 in doubly transfected human embryonic kidney cells (HEK cells) and in normal neuroblastoma cells, and both proteins could be coimmunoprecipitated from rat brain extracts, suggesting their close vicinity in vivo. Coexpression of MP100 and beta-APP695, however, did not boost A beta levels in HEK cells, although active enzyme was produced. Thus, MP100 does not exert true **beta-secretase**-like function in cells, although it may well act as a secondary exoprotease in a complex beta-APP/A beta metabolism.

L22 ANSWER 7 OF 48 MEDLINE DUPLICATE 4
ACCESSION NUMBER: 2000002972 MEDLINE
DOCUMENT NUMBER: 20002972 PubMed ID: 10531052
TITLE: **Beta-secretase** cleavage of Alzheimer's amyloid precursor protein by the transmembrane aspartic protease BACE.
COMMENT: Comment in: Science. 1999 Nov 12;286(5443):1254
Comment in: Science. 1999 Oct 22;286(5440):650-1
AUTHOR: Vassar R; Bennett B D; Babu-Khan S; Kahn S; Mendiaz E A; Denis P; Teplow D B; Ross S; Amarante P; Loeloff R; Luo Y; Fisher S; Fuller J; Edenson S; Lile J; Jarosinski M A; Biere A L; Curran E; Burgess T; Louis J C; Collins F; Treanor J; Rogers G; Citron M
CORPORATE SOURCE: Amgen, Inc., One Amgen Center Drive, M/S 29-2-B, Thousand Oaks, CA 91320-1799, USA.
SOURCE: SCIENCE, (1999 Oct 22) 286 (5440) 735-41. Journal code: 0404511. ISSN: 0036-8075.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)

LANGUAGE: English
FILE SEGMENT: Priority Journals
OTHER SOURCE: GENBANK-AF190725; GENBANK-AF190726; GENBANK-AF190727
ENTRY MONTH: 199911
ENTRY DATE: Entered STN: 20000111
Last Updated on STN: 20010604
Entered Medline: 19991105

AB Cerebral deposition of amyloid beta peptide (Abeta) is an early and critical feature of Alzheimer's disease. Abeta generation depends on proteolytic cleavage of the amyloid precursor protein (APP) by two unknown proteases: **beta-secretase** and gamma-secretase. These proteases are prime therapeutic targets. A transmembrane aspartic protease with all the known **characteristics** of **beta-secretase** was cloned and **characterized**. Overexpression of this protease, termed BACE (for beta-site APP-cleaving enzyme) increased the amount of **beta-secretase** cleavage products, and these were cleaved exactly and only at known **beta-secretase** positions. Antisense inhibition of endogenous BACE messenger RNA decreased the amount of **beta-secretase** cleavage products, and **purified** BACE protein cleaved APP-derived substrates with the same sequence specificity as **beta-secretase**. Finally, the expression pattern and subcellular localization of BACE were consistent with that expected for **beta-secretase**. Future development of BACE inhibitors may prove beneficial for the treatment of Alzheimer's disease.

L22 ANSWER 8 OF 48 MEDLINE DUPLICATE 5
ACCESSION NUMBER: 2000057171 MEDLINE
DOCUMENT NUMBER: 20057171 PubMed ID: 10591214
TITLE: **Purification** and cloning of amyloid precursor protein **beta-secretase** from human brain.
COMMENT: Comment in: Nature. 1999 Dec 2;402(6761):471-2
AUTHOR: Sinha S; Anderson J P; Barbour R; Basi G S; Caccavello R; Davis D; Doan M; Dovey H F; Frigon N; Hong J; Jacobson-Croak K; Jewett N; Keim P; Knops J; Lieberburg I; Power M; Tan H; Tatsuno G; Tung J; Schenk D; Seubert P; Suomensaari S M; Wang S; Walker D; John V; +
CORPORATE SOURCE: Elan Pharmaceuticals, South San Francisco, California 94080, USA. ssinha@elanpharama.com
SOURCE: NATURE, (1999 Dec 2) 402 (6761) 537-40.
Journal code: 0410462. ISSN: 0028-0836.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
OTHER SOURCE: GENBANK-AF201468
ENTRY MONTH: 199912
ENTRY DATE: Entered STN: 20000113
Last Updated on STN: 20000113
Entered Medline: 19991216

AB Proteolytic processing of the amyloid precursor protein (APP) generates amyloid beta (Abeta) peptide, which is thought to be causal for the pathology and subsequent cognitive decline in Alzheimer's disease. Cleavage by **beta-secretase** at the amino terminus of the Abeta peptide sequence, between residues 671 and 672 of APP, leads to the generation and extracellular release of beta-cleaved soluble APP, and a corresponding cell-associated carboxy-terminal fragment. Cleavage of the C-terminal fragment by gamma-secretase(s) leads to the formation of Abeta. The pathogenic mutation K670M671-->N670L671 at the **beta-secretase** cleavage site in APP, which was discovered in a Swedish family with familial Alzheimer's disease, leads to increased **beta-secretase** cleavage of the mutant substrate. Here we describe a membrane-bound enzyme activity that cleaves full-length APP at the **beta-secretase** cleavage site, and find it to be the predominant beta-cleavage activity in human brain. We have **purified** this enzyme activity to homogeneity from human brain using a new substrate analogue inhibitor of the enzyme activity, and show that the **purified** enzyme has all the properties predicted for **beta-secretase**. Cloning and expression of the enzyme reveals that human brain **beta-secretase** is a new

membrane-bound aspartic proteinase.

L22 ANSWER 9 OF 48 MEDLINE DUPLICATE 6
ACCESSION NUMBER: 2000120043 MEDLINE
DOCUMENT NUMBER: 20120043 PubMed ID: 10656250
TITLE: Identification of a novel aspartic protease (Asp 2) as **beta-secretase**.
AUTHOR: Hussain I; Powell D; Howlett D R; Tew D G; Meek T D; Chapman C; Gloger I S; Murphy K E; Southan C D; Ryan D M; Smith T S; Simmons D L; Walsh F S; Dingwall C; Christie G
CORPORATE SOURCE: Department of Neurosciences, SmithKline Beecham Pharmaceuticals, Harlow, Essex, United Kingdom.
SOURCE: MOLECULAR AND CELLULAR NEUROSCIENCES, (1999 Dec) 14 (6) 419-27.
Journal code: 9100095. ISSN: 1044-7431.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200002
ENTRY DATE: Entered STN: 20000229
Last Updated on STN: 20000229
Entered Medline: 20000217
AB The Alzheimer's disease beta-amyloid peptide (Abeta) is produced by excision from the type 1 integral membrane glycoprotein amyloid precursor protein (APP) by the sequential actions of beta- and then gamma-secretases. Here we report that Asp 2, a novel transmembrane aspartic protease, has the key activities expected of **beta-secretase**. Transient expression of Asp 2 in cells expressing APP causes an increase in the secretion of the N-terminal fragment of APP and an increase in the cell-associated C-terminal **beta-secretase** APP fragment. Mutation of either of the putative catalytic aspartyl residues in Asp 2 abrogates the production of the fragments **characteristic** of cleavage at the **beta-secretase** site. The enzyme is present in normal and Alzheimer's disease (AD) brain and is also found in cell lines known to produce Abeta. Asp 2 localizes to the Golgi/endoplasmic reticulum in transfected cells and shows clear colocalization with APP in cells stably expressing the 751-amino-acid isoform of APP.

L22 ANSWER 10 OF 48 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC. DUPLICATE 7
ACCESSION NUMBER: 2000:102367 BIOSIS
DOCUMENT NUMBER: PREV200000102367
TITLE: Genes and mechanisms involved in beta-amyloid generation and Alzheimer's disease.
AUTHOR(S): Steiner, H.; Capell, A.; Leimer, U.; Haass, C. (1)
CORPORATE SOURCE: (1) Adolf-Butenandt-Institute, Dept. of Biochemistry, Ludwig-Maximilians-University, D-80336, Munich Germany
SOURCE: European Archives of Psychiatry and Clinical Neuroscience, (Dec., 1999) Vol. 249, No. 6, pp. 266-270.
ISSN: 0940-1334.
DOCUMENT TYPE: Article
LANGUAGE: English
SUMMARY LANGUAGE: English
AB Alzheimer's disease is **characterized** by the invariable accumulation of senile plaques that are predominantly composed of amyloid beta-peptide (Abeta). Abeta is generated by proteolytic processing of the beta-amyloid precursor protein (betaAPP) involving the combined action of beta- and gamma-secretase. Cleavage within the Abeta domain by alpha-secretase prevents Abeta generation. In some very rare cases of familial AD (FAD), mutations have been identified within the betaAPP gene. These mutations are located close to or at the cleavage sites of the secretases and pathologically effect betaAPP processing by increasing Abeta production, specifically its highly amyloidogenic 42 amino acid variant (Abeta42). Most of the mutations associated with FAD have been identified in the two presenilin (PS) genes, particularly the PS1 gene. Like the mutations identified within the betaAPP gene, mutations in PS1 and PS2 cause the increased generation of Abeta42. PS1 has been shown to be functionally involved in Notch signaling, a key process in cellular differentation, and in betaAPP processing. A gene knock out of PS1 in mice

leads to an embryonic lethal phenotype similar to that of mice lacking Notch. In addition, absence of PS1 results in reduced gamma-secretase cleavage and leads to an accumulation of betaAPP C-terminal fragments and decreased amounts of Abeta. Recent work may suggest that PS1 could be the gamma-secretase itself, exhibiting the properties of a novel aspartyl protease. Mutagenesis of either of two highly conserved intramembraneous aspartate residues of PS1 leads to reduced Abeta production as observed in the PS1 knockout. A corresponding mutation in PS2 interfered with betaAPP processing and Notch signaling suggesting a functional redundancy of both presenilins.

L22 ANSWER 11 OF 48 CAPLUS COPYRIGHT 2003 ACS DUPLICATE 8
ACCESSION NUMBER: 1999:746382 CAPLUS
DOCUMENT NUMBER: 132:121009
TITLE: Guinea-pig primary cell cultures provide a model to study expression and amyloidogenic processing of endogenous amyloid precursor protein
AUTHOR(S): Beck, M.; Bruckner, M. K.; Holzer, M.; Kaap, S.; Pannicke, T.; Arendt, T.; Bigl, V.
CORPORATE SOURCE: Jahnallee 59, Paul Flechsig Institute for Brain Research, Department of Neurochemistry, University of Leipzig, Leipzig, D-04109, Germany
SOURCE: Neuroscience (Oxford) (1999), Volume Date 2000, 95(1), 243-254
CODEN: NRSCDN; ISSN: 0306-4522
PUBLISHER: Elsevier Science Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Until now guinea-pigs have been rarely used to investigate formation and deposition of Alzheimer's disease-assocd. amyloid .beta. peptides despite the sequence identity of human and guinea-pig amyloid .beta. peptides being known, and the overall similarity of human and guinea-pig amyloid precursor protein. We now describe a primary cell culture system of mixed fetal guinea-pig brain cells, which we have applied to **characterize** endogenous amyloid precursor protein processing and amyloid .beta. formation. These cell cultures were established at embryonic day 24 of guinea-pigs after comparison of selected stages of guinea-pig ontogenetic development with the known ontogeny of rats, and were **characterized** by immunocytochem. detection of neuronal and glial marker proteins. Amyloid precursor protein expression, processing and amyloid .beta. formation increased in parallel with cellular maturation during cultivation and reached a stable phase after approx. 14 days in vitro therefore providing a suitable time for anal. Aged cultures display strong neuronal amyloid precursor protein immunoreactivity and an altered profile of amyloid precursor protein isoform mRNA expression due to glial proliferation as single neurons were shown to retain their typical pattern of amyloid precursor protein expression. We show that amyloid precursor protein in guinea-pig cells is processed by different protease activities which most likely represent .alpha.- and .**beta**.-**secretase**, leading to the generation of sol. amyloid precursor protein derivs. Furthermore, endogenous amyloid precursor protein processing leads to prodn. of substantial amts. of amyloid .beta.-peptides which accumulate in conditioned culture medium. Amyloid .beta. was readily detectable by western blot anal. and was shown to consist of approx. 80-90% amyloid .beta.(1-40). We suggest that primary guinea-pig cell cultures provide a valuable tool in amyloid research that resembles amyloid precursor protein processing under physiol. concns. and, therefore, the situation in humans more closely than current rodent models. It should be esp. useful in screening expts. for secretase inhibiting compds.
REFERENCE COUNT: 100 THERE ARE 100 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L22 ANSWER 12 OF 48 MEDLINE DUPLICATE 9
ACCESSION NUMBER: 1999321864 MEDLINE
DOCUMENT NUMBER: 99321864 PubMed ID: 10393344
TITLE: Thimet oligopeptidase cleaves the full-length Alzheimer amyloid precursor protein at a **beta-secretase** cleavage site in COS cells.
AUTHOR: Koike H; Seki H; Kouchi Z; Ito M; Kinouchi T; Tomioka S;

Sorimachi H; Saido T C; Maruyama K; Suzuki K; Ishiura S
CORPORATE SOURCE: Department of Life Sciences, Graduate School of Arts and Sciences, The University of Tokyo, Meguro-ku, Tokyo, 153-8902, Japan.
SOURCE: JOURNAL OF BIOCHEMISTRY, (1999 Jul) 126 (1) 235-42.
Journal code: 0376600. ISSN: 0021-924X.
PUB. COUNTRY: Japan
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199910
ENTRY DATE: Entered STN: 20000111
Last Updated on STN: 20000111
Entered Medline: 19991028

AB We developed an assay method using a novel quenched fluorescent substrate (QFS) flanking the beta-cleavage site of amyloid precursor protein (APP), and **purified** a candidate **beta-secretase** from bovine brain. N-terminal amino acid analysis showed the candidate to be thimet oligopeptidase (TOP). The cDNA for human TOP was cloned from a human brain cDNA library and expressed in COS cells. The enzyme was further **purified** on a Ni2+-agarose column. TOP cleaved the Swedish Alzheimer's substrate (SEVNLDAEFR) as well as the normal substrate (SEVKMDAEFR). We then coexpressed TOP with APP695 in COS cells, collected transfected cells and conditioned media, and analyzed them by immunoblotting. The antibody against the specific secreted APP cleaved by **beta-secretase** (sAPPbeta) detected the secretion of sAPPbeta only from APP/hTOP-overexpressing cells, and not from cells overexpressing of antisense hTOP cDNA. Finally, we analyzed the immunolocalization of overexpressed hTOP in COS cells. Most hTOP was localized in the nuclei, but a small amount was localized in the Golgi or other organelles around the nuclei. These results suggest that TOP has a **beta-secretase**-like activity responsible for the processing of APP.

L22 ANSWER 13 OF 48 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2000:44900 CAPLUS
DOCUMENT NUMBER: 132:218674
TITLE: **Characterization** of .**beta**.-**secretase** using antibodies specific to the released N-terminus of .beta.-amyloid
AUTHOR(S): Austen, Brian M.; Frears, Emma R.; Stephens, David J.
CORPORATE SOURCE: Dept of Surgery, St. George's Hospital Medical School, London, SW17 0RE, UK
SOURCE: Innovation and Perspectives in Solid Phase Synthesis & Combinatorial Libraries: Peptides, Proteins and Nucleic Acids--Small Molecule Organic Chemical Diversity, Collected Papers, International Symposium, 5th, London, Sept. 2-6, 1997 (1999), Meeting Date 1997, 177-180. Editor(s): Epton, Roger. Mayflower Scientific Ltd.: Kingswinford, UK.
CODEN: 68OEAA
DOCUMENT TYPE: Conference
LANGUAGE: English

AB Major constituents of senile plaques found in the brains of Alzheimer's patients are 39-43 residue peptides known as .beta.-amyloid, which have been shown to be toxic to neurons cultured in vitro. In familial Alzheimer's disease, rare mutations in the amyloid precursor protein gene on chromosome 21, or in the presenilin genes on chromosomes 1 and 14 give rise to increased amts. of .beta.-amyloid, particularly the longer form .beta.-amyloid 1-42. As senile plaques are an invariant feature of Alzheimer's disease, increased prodn. of .beta.-amyloid may be an important pathol. feature of the more common sporadic as well as familial form of Alzheimer's disease. The major site of cleavage is at Asp672 in the amyloid precursor protein (APP) 695, or Aspl numbered as the N-terminal residue of .beta.-amyloid in between a Met-Asp sequence, by an enzyme termed .**beta**.-**secretase**. .**beta**.-**Secretase** has not been **characterized**, but clearly represents a potential therapeutic target. To identify .**beta**.-**secretase**, we have raised affinity-**purified** antibody directed to the cleaved N-terminus of .beta.-amyloid with a synthetic peptide of the N-terminal ten residues of .beta.-amyloid coupled via a

C-terminal Cys residue to a protein carrier, which does not cross-react with APP.

REFERENCE COUNT: 10 THERE ARE 10 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L22 ANSWER 14 OF 48 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 1999041419 EMBASE
TITLE: Inhibition of .beta.-amyloid formation as a therapeutic strategy.
AUTHOR: Moore C.L.; Wolfe M.S.
CORPORATE SOURCE: M.S. Wolfe, Department of Pharmaceutical Science, University of Tennessee, 847 Monroe Avenue, Memphis, TN 38163, United States. mwolfe@utmem.edu
SOURCE: Expert Opinion on Therapeutic Patents, (1999) 9/2 (135-146).
Refs: 84
ISSN: 1354-3776 CODEN: EOTPEG
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 008 Neurology and Neurosurgery
030 Pharmacology
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English
AB A considerable body of evidence has accumulated in recent years implicating the .beta.-amyloid protein (A.beta.) in the aetiology of Alzheimer's disease (AD). The highly hydrophobic A.beta. can nucleate and form neurotoxic fibrils which are **characteristic** components of AD neuritic plaques. Three general strategies for preventing or slowing the A.beta.-initiated cascade of events leading to AD are (1) block the downstream signalling pathways that result in cytotoxic responses to A.beta. fibrils, (2) interfere with A.beta. nucleation and fibrillogenesis, and (3) inhibit the proteolytic events that lead to A.beta. generation. In this article, we provide a perspective on the current knowledge of the molecular basis of AD, discuss the advantages of the third therapeutic strategy, blocking A.beta. production, and review the recent journal and patent literature describing compounds that work at this level. Finally, we will discuss the most pressing issues that need to be addressed in order to more effectively develop useful therapeutic agents that lower A.beta. concentrations in the central nervous system (CNS).

L22 ANSWER 15 OF 48 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1998:406069 CAPLUS
DOCUMENT NUMBER: 129:78491
TITLE: **Beta-secretase isolation** from human 293 cells and cleavage of beta-amyloid precursor protein
INVENTOR(S): Chrysler, Susanna M. S.; Sinha, Sukanto; Keim, Pamela S.; Anderson, John P.
PATENT ASSIGNEE(S): Athena Neurosciences, Inc., USA; Chrysler, Susanna M. S.; Sinha, Sukanto; Keim, Pamela S.; Anderson, John P.
SOURCE: PCT Int. Appl., 40 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9826059	A1	19980618	WO 1996-US19549	19961211
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, US, UZ, VN, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: KE, LS, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
AU 9716840	A1	19980703	AU 1997-16840	19961211

PRIORITY APPLN. INFO.: WO 1996-US19549 19961211

AB The present invention provides a novel .**beta.-secretase** compn. comprising an **isolated** and **purified** enzyme which cleaves .beta.-amyloid precursor protein (APP) at the amino-terminus of .beta.-amyloid peptide (.beta.AP) within APP. The .**beta.-secretase** has an apparent MW from about 260-300 kDa, when glycosylated and binds wheat germ agglutinin. A screening assay for identification of .**beta.-secretase** inhibitors shows that the .**beta.-secretase** is not inhibited by common inhibitors of serine, cysteine, aspartyl and metalloproteases. The compns. of the present invention are generally useful as proteolytic chems. and specifically useful in assays for detg. whether a test substance will inhibit proteolytic cleavage of APP resulting from the novel .**beta.-secretase**.

REFERENCE COUNT: 6 THERE ARE 6 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L22 ANSWER 16 OF 48 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.

ACCESSION NUMBER: 1998:341993 BIOSIS

DOCUMENT NUMBER: PREV199800341993

TITLE: Amyloid precursor protein processing in sterol regulatory element-binding protein site 2 protease-deficient Chinese hamster ovary cells.

AUTHOR(S): Ross, Sandra L.; Martin, Francis; Simonet, Lizette; Jacobsen, Frederick; Deshpande, Rohini; Vassar, Robert; Bennett, Brian; Luo, Yi; Wooden, Scott; Hu, Sylvia; Citron, Martin; Burgess, Teresa L. (1)

CORPORATE SOURCE: (1) Dep. Mammalian Cell Molecular Biol., Amgen Inc., One Amgen Center Dr., Thousand Oaks, CA 91320-1789 USA

SOURCE: Journal of Biological Chemistry, (June 19, 1998) Vol. 273, No. 25, pp. 15309-15312.
ISSN: 0021-9258.

DOCUMENT TYPE: Article

LANGUAGE: English

AB Amyloid peptides of 39-43 amino acids (Abeta) are the major constituents of amyloid plaques present in the brains of Alzheimer's (AD) patients. Proteolytic processing of the amyloid precursor protein (APP) by the yet unidentified beta- and gamma-secretases leads to the generation of the amyloidogenic Abeta peptides. Recent data suggest that all of the known mutations leading to early onset familial AD alter the processing of APP such that increased amounts of the 42-amino acid form of Abeta are generated by a gamma-secretase activity. Identification of the beta- and/or gamma-secretases is a major goal of current AD research, as they are prime targets for therapeutic intervention in AD. It has been suggested that the sterol regulatory element-binding protein site 2 protease (S2P) may be identical to the long sought gamma-secretase. We have directly tested this hypothesis using over-expression of the S2P cDNA in cells expressing APP and by **characterizing** APP processing in mutant Chinese hamster ovary cells that are deficient in S2P activity and expression. The data demonstrate that S2P does not play an essential role in the generation or secretion of Abeta peptides from cells, thus it is unlikely to be a gamma-secretase.

L22 ANSWER 17 OF 48 SCISEARCH COPYRIGHT 2003 ISI (R)

ACCESSION NUMBER: 1998:430982 SCISEARCH

THE GENUINE ARTICLE: ZQ947

TITLE: Regulation of amyloid precursor protein seer receptors in human Ntera 2 neurons (NT2N)

AUTHOR: JollyTornetta C; Gao Z Y; Lee V M Y; Wolf B A (Reprint)

CORPORATE SOURCE: UNIV PENN, SCH MED, DEPT PATHOL & LAB MED, 230 JOHN MORGAN BLDG, 3620 HAMILTON WALK, PHILADELPHIA, PA 19104 (Reprint); UNIV PENN, SCH MED, DEPT PATHOL & LAB MED, PHILADELPHIA, PA 19104

COUNTRY OF AUTHOR: USA

SOURCE: JOURNAL OF BIOLOGICAL CHEMISTRY, (29 MAY 1998) Vol. 273, No. 22, pp. 14015-14021.
Publisher: AMER SOC BIOCHEMISTRY MOLECULAR BIOLOGY INC, 9650 ROCKVILLE PIKE, BETHESDA, MD 20814.
ISSN: 0021-9258.

DOCUMENT TYPE: Article; Journal

FILE SEGMENT: LIFE

LANGUAGE: English
REFERENCE COUNT: 44
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB The amyloid precursor protein (APP) can be cleaved by a **beta-secretase** to generate a beta-amyloid peptide, which has been implicated in the pathogenesis of Alzheimer's disease. However, APP can also be cleaved by an alpha-secretase to form a non-amyloidogenic secreted form of APP (APP-S). APP-S secretion can be physiologically regulated. This study examined the glutamatergic regulation of APP in the human neuronal Ntera 2 (NT2N) cell line.

Metabotropic glutamate receptor subtypes 1 alpha/beta and 5 alpha were identified in the NT2N neurons by reverse transcription-polymerase chain reaction. Stimulation of these phosphatidylinositol-linked receptors with glutamate or specific receptor agonists resulted in a dose- and time-dependent increase in the secretion of the amyloid precursor protein (APP-S), measured by the immunoprecipitation of APP-S from the medium of [S-35]methionine-labeled NT2N neurons. The glutamate-induced APP-S secretion was maximal at 30 min and at a concentration of 1 mM glutamate, Glutamate-induced APP-S secretion required activation of phospholipase C, which resulted in inositol 1,4,5-trisphosphate production, as shown by the rapid glutamate-induced accumulation of inositol 1,4,5-trisphosphate, Glutamate also caused an increase in intracellular Ca2+, The protein kinase C activator phorbol 12-myristate 13-acetate, a phorbol ester, as well as 1-oleoyl-2-acetoyl-3-glycerol, a cell-permeable diacylglycerol analog, also stimulated APP-S secretion. These findings suggest that APP-S secretion from NT2N neurons can be regulated by the activation of phosphatidylinositol-linked metabotropic glutamate receptor signaling pathway.

L22 ANSWER 18 OF 48 MEDLINE DUPLICATE 10
ACCESSION NUMBER: 1998448529 MEDLINE
DOCUMENT NUMBER: 98448529 PubMed ID: 9775403
TITLE: The regulation of amyloid precursor protein metabolism by cholinergic mechanisms and neurotrophin receptor signaling.
AUTHOR: Rossner S; Ueberham U; Schliebs R; Perez-Polo J R; Bigl V
CORPORATE SOURCE: Paul Flechsig Institute for Brain Research, Department of Neurochemistry, University of Leipzig, Germany.
SOURCE: PROGRESS IN NEUROBIOLOGY, (1998 Dec) 56 (5) 541-69. Ref: 286
Journal code: 0370121. ISSN: 0301-0082.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, ACADEMIC)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199812
ENTRY DATE: Entered STN: 19990115
Last Updated on STN: 20000303
Entered Medline: 19981230

AB The increased expression and/or abnormal processing of the amyloid precursor protein (APP) is associated with the formation of amyloid plaques and cerebrovascular amyloid deposits, which are one of the major morphological hallmarks of Alzheimer's disease (AD). Among the processes regulating APP metabolism, the proteolytic cleavage of APP into amyloidogenic or nonamyloidogenic fragments is of special interest. The cleavage of the APP by the alpha-secretase within the beta-amyloid sequence generates nonamyloidogenic C-terminal APP fragments and soluble APPs alpha, which has neurotrophic and neuroprotective activities. Proteolytic processing of APP by **beta-secretase**, on the other hand, exposes the N-terminus of beta-amyloid, which is liberated after gamma-secretase cleavage at the variable amyloid C-terminus. The resulting 39-43 amino acid beta-amyloid may be neurotoxic and disrupt neuronal connectivity after its accumulation in senile plaques. In this review, we discuss evidence derived from in vitro experiments, suggesting that the stimulation of protein kinase C (PKC)-coupled M1/M3 muscarinic acetylcholine receptors increases the nonamyloidogenic, secretory pathway of APP processing. It has also been shown in animal models that under conditions of reduced M1/M3 muscarinic acetylcholine receptor stimulation the secretory pathway of APP processing is inhibited and that constitutive upregulation of M1/M3-associated PKC increases APP secretion. Thus, the

cortical cholinergic hypoactivity **characteristic** of AD may inhibit the nonamyloidogenic APP processing pathway and lead to increased beta-amyloid generation. It has been shown in vitro that nerve growth factor (NGF)-associated signaling also influences the expression and catabolism of APP. Recent experiments with NGF-responsive cells revealed a specific role for the high-affinity NGF receptor, TrkA, in the increases in secretory APP processing and a role for the low-affinity neurotrophin receptor, p75NTR, in the transcriptional regulation of APP. Therefore, treatments with NGF could ameliorate cortical cholinergic dysfunction in AD. These findings may influence the design of therapeutic strategies aimed at stimulating cholinergic function and at increasing nonamyloidogenic APP processing without elevating APP expression.

L22 ANSWER 19 OF 48 MEDLINE DUPLICATE 11
ACCESSION NUMBER: 1998439041 MEDLINE
DOCUMENT NUMBER: 98439041 PubMed ID: 9765904
TITLE: **Characterization** of **beta-secretase**.
AUTHOR: Stephens D J; Austen B M
CORPORATE SOURCE: Department of Surgery, St George's Hospital Medical School, London, UK.
SOURCE: BIOCHEMICAL SOCIETY TRANSACTIONS, (1998 Aug) 26 (3) 500-4. Ref: 21
Journal code: 7506897. ISSN: 0300-5127.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199812
ENTRY DATE: Entered STN: 19990115
Last Updated on STN: 20000303
Entered Medline: 19981211

L22 ANSWER 20 OF 48 MEDLINE DUPLICATE 12
ACCESSION NUMBER: 1999049150 MEDLINE
DOCUMENT NUMBER: 99049150 PubMed ID: 9832310
TITLE: Effect of oxidation of beta-amyloid precursor protein on its **beta-secretase** cleavage. A model study with synthetic peptides and candidate **beta-secretases**.
AUTHOR: Rapala-Kozik M; Kozik A; Travis J
CORPORATE SOURCE: Institute of Molecular Biology, Jagiellonian University, Krakow, Poland.
SOURCE: JOURNAL OF PEPTIDE RESEARCH, (1998 Oct) 52 (4) 315-20.
Journal code: 9707067. ISSN: 1397-002X.
PUB. COUNTRY: Denmark
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199901
ENTRY DATE: Entered STN: 19990209
Last Updated on STN: 20000303
Entered Medline: 19990127

AB As the amyloidogenic processing of beta-amyloid precursor protein (betaAPP) proceeds under conditions of oxidative stress, the methionine-596 residue at the **beta-secretase** cleavage point is likely in an oxidized state. In the present work, possible consequences of the oxidation of Met-596 for the generation of the N-terminus of amyloid beta protein were modeled using synthetic peptide substrates, matching 587-606 sequence fragment of betaAPP and containing either intact methionine or methionine sulfoxide. Patterns and rates for the cleavage of these substrates by **purified** mast cell chymase, cathepsin G, cathepsin D, matrix metalloproteinase-3 and neutrophil elastase, were compared. Only the three first proteases, all previously suggested as candidate **beta-secretases**, preferentially cleaved the "intact" substrate after Met-596. For chymase and cathepsin G, the specificity of this cleavage increased upon a shift from optimal alkaline pH to acidic pH, which is also more compatible with the plausible intracellular localization of amyloidogenic betaAPP processing. The

substitution of methionine sulfoxide for methionine in the substrate slowed down the cleavage rate for all the enzymes tested, by a factor of 6-15. This was associated with shifts of cleavage preferences to points of minor importance for the "intact" peptide, suggesting a specific resistance of the peptide bond after MetSO-596 against proteolysis.

L22 ANSWER 21 OF 48 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1998:588525 CAPLUS
DOCUMENT NUMBER: 129:299493
TITLE: Molecular **characterization** of the Alzheimer's amyloid precursor protein secretases
AUTHOR(S): Houldsworth, Sarah L.; Trew, Alison J.; Hooper, Nigel M.; Turner, Anthony J.
CORPORATE SOURCE: School of Biochemistry and Molecular Biology, University of Leeds, Leeds, LS2 9JT, UK
SOURCE: Biochemical Society Transactions (1998), 26(3), S245
CODEN: BCSTB5; ISSN: 0300-5127
PUBLISHER: Portland Press Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Alzheimer's disease is the archetypal form of senile dementia. In the amyloidogenic pathway the combined proteolytic activity of .**beta** .-**secretase** at the N-terminus and .gamma.-secretase(s) at the C-terminus of .beta.A4 releases the intact peptide. Here, we describe the development of a cell-free assay for the .alpha.- and .**beta**.-**secretases** utilizing fusion protein constructs of the carboxyl-terminal region of the .beta.-amyloid precursor protein attached to the ectodomain of a detectable enzyme species.
REFERENCE COUNT: 6 THERE ARE 6 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L22 ANSWER 22 OF 48 LIFESCI COPYRIGHT 2003 CSA DUPLICATE 13
ACCESSION NUMBER: 1999:76930 LIFESCI
TITLE: Products of the Alzheimer's disease amyloid precursor protein generated by **beta -secretase** are present in human platelets, and secreted upon degranulation
AUTHOR: Li, Qiao-Xin; Cappai, R.; Evin, G.; Tanner, J.E.; Gray, C.W.; Beyreuther, K.; Masters, C.L.
CORPORATE SOURCE: Department of Pathology, University of Melbourne, Parkville, Victoria, Australia
SOURCE: American Journal of Alzheimer's Disease [Am. J. Alzheimer's Dis.], (19981000) vol. 13, no. 5, pp. 236-244.
ISSN: 1082-5207.
DOCUMENT TYPE: Journal
FILE SEGMENT: N3
LANGUAGE: English
SUMMARY LANGUAGE: English
AB Proteolytic processing of Alzheimer's disease amyloid precursor protein (APP) by **beta -secretase** generates the N-terminus of A beta (which deposits in the brain) and releases a secreted ectodomain of APP (sAPP beta). We identified in human platelets a band at similar to 125 kDa corresponding to APP ectodomain ending with C-terminal methionine residue (APP super(671)) as **characterized** by an antibody specific for the C-terminal methionine residue of sAPP beta . The same antibody also detected bands at similar to 105 and similar to 125 kDa in human brain homogenates. Platelet sAPP beta is an isoform containing the Kunitz protease inhibitor domain (sAPP beta -KPI super(+)) and is released into the medium when platelets are induced to aggregate using agonists such as thrombin, collagen, phorbol 12-myristate 13-acetate, or calcium ionophore A23187. The release of sAPP beta from aggregated platelets is consistent with a role in regulation of the coagulation cascade and/or in platelet aggregation. These data together with previous reports suggest that human platelets contain the alpha -, beta - and gamma -secretase activities, and are a suitable system to study APP processing and A beta production, a pathway which is considered to be a prime target for therapeutic intervention in AD.

L22 ANSWER 23 OF 48 MEDLINE DUPLICATE 14
ACCESSION NUMBER: 97461617 MEDLINE
DOCUMENT NUMBER: 97461617 PubMed ID: 9315893

TITLE: Late compartments of amyloid precursor protein transport in SY5Y cells are involved in beta-amyloid secretion.
AUTHOR: Peraus G C; Masters C L; Beyreuther K
CORPORATE SOURCE: Center for Molecular Biology Heidelberg, The University of Heidelberg, D-69120 Heidelberg, Germany.
SOURCE: JOURNAL OF NEUROSCIENCE, (1997 Oct 15) 17 (20) 7714-24. Journal code: 8102140. ISSN: 0270-6474.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199710
ENTRY DATE: Entered STN: 19971105
Last Updated on STN: 19971105
Entered Medline: 19971023

AB Amyloid plaques, composed mainly of the 39-43 amino acid betaA4 peptide, are a **characteristic** feature of Alzheimer's disease. Generation of betaA4 by proteolytic processing of the amyloid precursor protein (APP) is thought to occur in a pathway that includes the activity of two as yet unknown proteases, with **beta-secretase** cleaving at the N terminus and gamma-secretase releasing the C terminus of betaA4. Inhibition studies and the finding that cell surface APP can serve as a direct precursor of betaA4 suggest that the endosomal/lysosomal compartment is involved in the proteolysis of APP into betaA4. In this study we targeted APP695 chimeric proteins directly into the endosomal/lysosomal compartment. This decreased the amount of released betaA4, while the generation of the betaA4 N terminus continued. APP695 proteins were constructed also, which carried sorting signals responsible for recycling between the trans-Golgi network (TGN) and the cell surface. These proteins were processed into secreted betaA4 at even higher levels than wild-type APP695. Moreover, retention of APP695 proteins in the endoplasmic reticulum led to neither betaA4 secretion nor to processing by **beta-secretase** in human SH-SY5Y neuroblastoma cells. These data suggest that a beta-cleavage activity resides in a late endosomal compartment and that a gamma-cleavage occurs in early endosomes, resulting in the generation of betaA4 peptides with the majority ending at residue 40.

L22 ANSWER 24 OF 48 MEDLINE DUPLICATE 15
ACCESSION NUMBER: 97392695 MEDLINE
DOCUMENT NUMBER: 97392695 PubMed ID: 9245794
TITLE: Novel **beta-secretase** cleavage of beta-amyloid precursor protein in the endoplasmic reticulum/intermediate compartment of NT2N cells.
AUTHOR: Chyung A S; Greenberg B D; Cook D G; Doms R W; Lee V M
CORPORATE SOURCE: Department of Pathology and Laboratory Medicine, University of Pennsylvania School of Medicine, Philadelphia, Pennsylvania 19104, USA.
CONTRACT NUMBER: AG-11542 (NIA)
SOURCE: JOURNAL OF CELL BIOLOGY, (1997 Aug 11) 138 (3) 671-80. Journal code: 0375356. ISSN: 0021-9525.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199708
ENTRY DATE: Entered STN: 19970908
Last Updated on STN: 20000303
Entered Medline: 19970828

AB Previous studies have demonstrated that NT2N neurons derived from a human embryonal carcinoma cell line (NT2) constitutively process the endogenous wild-type beta-amyloid precursor protein (APP) to amyloid beta peptide in an intracellular compartment. These studies indicate that other proteolytic fragments generated by intracellular processing must also be present in these cells. Here we show that the NH2-terminal fragment of APP generated by **beta-secretase** cleavage (APPbeta) is indeed produced from the endogenous full length APP (APPFL). Pulse-chase studies demonstrated a precursor-product relationship between APPFL and APPbeta as well as intracellular and secreted APPbeta fragments. In addition, trypsin digestion of intact NT2N cells at 4 degrees C did not abolish APPbeta recovered from the cell lysates. Furthermore, the

production of intracellular APPbeta from wild-type APP appears to be a unique **characteristic** of postmitotic neurons, since intracellular APPbeta was not detected in several non-neuronal cell lines. Significantly, production of APPbeta occurred even when APP was retained in the ER/ intermediate compartment by inhibition with brefeldin A, incubation at 15 degrees C, or by expression of exogenous APP bearing the dilysine ER retrieval motif.

L22 ANSWER 25 OF 48 MEDLINE DUPLICATE 16
ACCESSION NUMBER: 97322910 MEDLINE
DOCUMENT NUMBER: 97322910 PubMed ID: 9179400
TITLE: Examination of the role of endopeptidase 3.4.24.15 in A beta secretion by human transfected cells.
AUTHOR: Chevallier N; Jiracek J; Vincent B; Baur C P; Spillantini M G; Goedert M; Dive V; Checler F
CORPORATE SOURCE: Institut de Pharmacologie Moleculaire et Cellulaire, UPR411 du CNRS, Valbonne, France.
SOURCE: BRITISH JOURNAL OF PHARMACOLOGY, (1997 Jun) 121 (3) 556-62.
Journal code: 7502536. ISSN: 0007-1188.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199708
ENTRY DATE: Entered STN: 19970813
Last Updated on STN: 20000303
Entered Medline: 19970804

AB 1. We have taken advantage of our recent development of highly potent and specific phosphinic inhibitors of endopeptidase 3.4.24.15 to examine the putative contribution of the enzyme in the secretion of A beta by HK293 transfected cells overexpressing the wild type and the Swedish (Sw) double mutated form of beta APP751. 2. First, we showed that HK293 cells contain a peptidase activity, the inhibition profile of which fully matches that of **purified** endopeptidase 3.4.24.15. Second, we established that the treatment of HK293 cells with specific phosphinic inhibitors leads to about 80% inhibition of intracellular endopeptidase 3.4.24.15 activity, indicating that these inhibitors penetrate the cells. 3. Metabolic labelling of wild type and Sw beta APP751-expressing cells, followed by immunoprecipitation of A beta-containing peptides, revealed the secretion of A beta and the intracellular formation of an A beta-containing 12 kDa product. 4. A beta secretion by Sw beta APP751 transfected cells was drastically enhanced when compared to cells expressing wild type beta APP751. This production was not affected by endopeptidase 3.4.24.15 inhibitors in either cell type. This correlates well with the observation that endopeptidase 3.4.24.15 does not cleave recombinant baculoviral Sw beta APP751, in vitro. 5. Our previous data indicated that endopeptidase 3.4.24.15 activity was reduced in the parietal cortex of Alzheimer's disease affected brains and that the enzyme probably participated, in this brain area, to the catabolism of somatostatin 1-14. However, the present work indicates that endopeptidase 3.4.24.15 does not seem to behave as a **beta-secretase** in HK293 transfected cells. Therefore, it is suggested that endopeptidase 3.4.24.15 could participate in the symptomatology, but probably not in the aetiology of Alzheimer's disease.

L22 ANSWER 26 OF 48 MEDLINE
ACCESSION NUMBER: 97470298 MEDLINE
DOCUMENT NUMBER: 97470298 PubMed ID: 9329715
TITLE: Effects of cholinesterase inhibitors on the secretion of beta-amyloid precursor protein in cell cultures.
AUTHOR: Lahiri D K; Farlow M R; Nurnberger J I Jr; Greig N H
CORPORATE SOURCE: Department of Psychiatry, Indiana University School of Medicine, Indianapolis 46202, USA..
DLAHIRI@INDYVAX.IUPUI.EDU
SOURCE: ANNALS OF THE NEW YORK ACADEMY OF SCIENCES, (1997 Sep 26) 826 416-21.
Journal code: 7506858. ISSN: 0077-8923.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199711

ENTRY DATE: Entered STN: 19971224
Last Updated on STN: 19971224
Entered Medline: 19971113

AB One of the main **characteristics** of Alzheimer's disease (AD) is the cerebrovascular deposition of the amyloid beta-peptide (A beta), which is derived from a larger beta-amyloid precursor protein (beta APP). The majority of beta APP is processed by either a secretory of lysosomal/endosomal pathway. Carboxyl-truncated soluble derivatives of beta APP (sAPP) are generated by the proteolytic processing of full-length beta APP by either alpha- or **beta-secretase** enzyme.
Our objective is to determine whether the processing of beta APP can be regulated by cholinesterase inhibitors, some of which were shown to produce a moderate improvement in memory and cognitive functions in patients with Alzheimer's disease. Here we have analyzed the levels of sAPP derivatives in cultured cells treated with different drugs by immunoblotting samples of conditioned media. The immunoreactive protein bands were developed by probing with the monoclonal antibody 22C11. Treating neuroblastoma, pheochromocytoma and fibroblast cells with high dose of either 3,4-diaminopyridine, metrifonate, or physostigmine did not inhibit the secretion of sAPP. Treating glioblastoma with either 3,4-diaminopyridine or metrifonate showed an increase in secretion of sAPP. However, treatment of cells with tacrine reduced release of sAPP in conditioned media of cell lines studied. The difference in action of metrifonate, physostigmine, and tacrine on beta APP is independent of their anticholinesterase activities. Our results suggests that noncatalytic functions of cholinesterase inhibitors can be utilized to alter the metabolism of beta APP, which might in turn affect the process of deposition of A beta, a key component of the cerebrovascular amyloid detected in AD.

L22 ANSWER 27 OF 48 SCISEARCH COPYRIGHT 2003 ISI (R) DUPLICATE 17
ACCESSION NUMBER: 97:213384 SCISEARCH
THE GENUINE ARTICLE: WL803
TITLE: A possible role for cathepsins D, E, and B in the processing of beta-amyloid precursor protein in Alzheimer's disease
AUTHOR: Mackay E A (Reprint); Ehrhard A; Moniatte M; Guenet C; Tardif C; Tarnus C; Sorokine O; Heintzelmann B; Nay C; Remy J M; Higaki J; VanDorsselaer A; Wagner J; Danzin C; Mamont P
CORPORATE SOURCE: 1 CASWALL CLOSE, FOXLEY FIELDS, BINFIELD RG42 4EF, BERKS, ENGLAND (Reprint); MARION MERRELL DOW RES INST, STRASBOURG, FRANCE; UNIV STRASBOURG 1, LSMBO, STRASBOURG, FRANCE; SCIOS NOVA INC, MT VIEW, CA 94043
COUNTRY OF AUTHOR: ENGLAND; FRANCE; USA
SOURCE: EUROPEAN JOURNAL OF BIOCHEMISTRY, (1 MAR 1997) Vol. 244, No. 2, pp. 414-425.
Publisher: SPRINGER VERLAG, 175 FIFTH AVE, NEW YORK, NY 10010.
ISSN: 0014-2956.
DOCUMENT TYPE: Article; Journal
FILE SEGMENT: LIFE
LANGUAGE: English
REFERENCE COUNT: 59
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB Formation of the 4-kDa peptides, which are essential constituents of the extracellular plaques in Alzheimer's disease, involves the sequential cleavage of the amyloid precursor protein (APP) by beta- and gamma-secretases. The carboxy-terminal 99-amino-acid peptide which is liberated from APP by **beta-secretase** was used as a potential native substrate of the gamma-secretase(s). With the addition of an initiator Met and a FLAG sequence at the C-terminus (beta APP100-FLAG), it was expressed in Escherichia coli under the control of the T7 promotor. The preferred site(s) of cleavage in the N-terminal 30-amino-acid beta-amyloid peptide and beta APP100-FLAG by potential gamma-secretase(s) were rapidly identified using matrix-assisted laser-desorption/ionization time-of-flight mass spectroscopy in addition to peptide mapping followed by protein sequence analysis. Since gamma-secretases seem to be active at acidic pH, three cathepsins (D, E and B) were selected for testing. Studies using different detergents indicated that the cleavage preference of cathepsin D for the beta APP100-FLAG is highly dependent on the

surfactant used to solubilize this substrate. All three cathepsins were found to be capable of catabolizing both beta-amyloid peptides and the beta APP100-FLAG. As cathepsin D was found to cleave the beta APP100-FLAG in the vicinity of the C-terminus of the beta-amyloid peptides and cathepsin B has a high carboxypeptidase activity at low pH, the possibility cannot be excluded that cathepsins D and B are involved in the amyloidogenic processing of APP.

L22 ANSWER 28 OF 48 MEDLINE DUPLICATE 18
ACCESSION NUMBER: 97473875 MEDLINE
DOCUMENT NUMBER: 97473875 PubMed ID: 9332717
TITLE: Expression and **characterization** of human **beta-secretase** candidates metalloendopeptidase MP78 and cathepsin D in beta APP-overexpressing cells.
AUTHOR: Thompson A; Grueninger-Leitch F; Huber G; Malherbe P
CORPORATE SOURCE: Pharma Division, F. Hoffmann-La Roche Ltd., Basel, Switzerland.
SOURCE: BRAIN RESEARCH. MOLECULAR BRAIN RESEARCH, (1997 Sep) 48 (2) 206-14.
Journal code: 8908640. ISSN: 0169-328X.
PUB. COUNTRY: Netherlands
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199802
ENTRY DATE: Entered STN: 19980226
Last Updated on STN: 20000303
Entered Medline: 19980217
AB Human **beta-secretase** candidates, MP78 (h-MP78, EC 3.4.24.15) and cathepsin D (Cat D, EC 3.4.23.5), were evaluated for their ability to enhance amyloid-beta-protein (A beta) secretion when overexpressed in beta APP-containing cells. HEK-293 cells stably co-expressing h-MP78 or Cat D and h-beta APP695 were metabolically labeled with [35S]methionine and A beta secretion was quantified in the conditioned media by immunoprecipitation and ELISA without showing any significant increase in A beta production. Because Cat D is known to have a higher affinity for APP-substrate containing the Swedish familial Alzheimer's disease double mutation (SFAD, K595N and M596L substitutions in beta APP695) than for the wild type substrate [Dreyer et al., Eur. J. Biochem., 224 (1994) 265-271], the effect of Cat D overexpression was tested in a HEK293/beta APPSFAD stable cell line. ELISA analysis of the conditioned media from these cells did also not reveal any increase in A beta generation. In addition, recombinant h-MP78 **purified** from E. coli cleaved an APP-derived substrate spanning the **beta-secretase** site (ISEVKMD1AEFRHDS) at multiple sites, but the beta-site cleavage was only a minor one; cleavage occurred predominantly at K-M and E-F bonds. Human liver Cat D also cleaved the same substrate at multiple sites, yet the major cleavage at pH 4.0 occurred at the amyloidogenic D1 site. These findings indicate that h-MP78 does not have the cleavage specificity required for a **beta-secretase** protease and although Cat D fulfilled the amyloidogenic cleavage specificity, the results of the co-expression experiments make both enzymes less likely candidates as relevant **beta-secretases**.

L22 ANSWER 29 OF 48 MEDLINE DUPLICATE 19
ACCESSION NUMBER: 97253081 MEDLINE
DOCUMENT NUMBER: 97253081 PubMed ID: 9098524
TITLE: Cathepsin D displays in vitro **beta-secretase**-like specificity.
AUTHOR: Chevallier N; Vizzavona J; Marambaud P; Baur C P; Spillantini M; Fulcrand P; Martinez J; Goedert M; Vincent J P; Checler F
CORPORATE SOURCE: Institut de Pharmacologie Moleculaire et Cellulaire, CNRS, Valbonne, France.
SOURCE: BRAIN RESEARCH, (1997 Mar 7) 750 (1-2) 11-9.
Journal code: 0045503. ISSN: 0006-8993.
PUB. COUNTRY: Netherlands
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English

FILE SEGMENT: Priority Journals
ENTRY MONTH: 199706
ENTRY DATE: Entered STN: 19970630
Last Updated on STN: 20000303
Entered Medline: 19970617

AB The formation of A beta and A beta-containing fragments is likely a key event in the process of neural degeneration in Alzheimer's disease. The N-terminal residue (Asp-1) of A beta and its C-terminally extended sequences is liberated from the beta-amyloid precursor protein (beta APP) by **beta-secretase**(s). This activity appears highly increased by the presence (N-terminally to Asp-1) of a double-mutation (KM-->NL) found in several Swedish families affected by early onset Alzheimer's disease. By means of synthetic peptides encompassing the "normal' (N peptide) and mutated (delta NL peptide) sequences targeted by **beta-secretase**(s), we have detected a human brain protease displaying preferred efficiency for the delta NL peptide than for the non-mutated analog. This activity is sensitive to pepstatin, maximally active at acidic pH and hydrolyses the two peptides at the expected M/D or L/D cleavage sites. Such acidic activity is also detected in rat brain, PC12 cells and primary cultured astrocytes. The pepstatin sensitivity and pH maximum of the brain activity that appeared reminiscent of those displayed by the acidic protease cathepsin D led us to examine this enzyme as a putative **beta-secretase**-like candidate.
Purified cathepsin D displays higher catalytic parameters for the delta NL peptide than for the non-mutated peptide, cleaves these two substrates at the expected M/D or L/D sites, and is maximally active at acidic pH. However, cathepsin D does not cleave peptides bearing mutations that were previously shown to drastically lower or fully block A beta secretion by transfected cells. Furthermore, cathepsin D hydrolyses recombinant baculoviral delta NL beta APP751 at a 6-fold higher rate than beta APP751 and gives rise to a 12-kDa C-terminal product that is recognized by antibodies fully specific of the N-terminus of A beta. Altogether, our study indicates that cathepsin D displays several in vitro **beta-secretase**-like properties that suggests that this protease could fulfill such a role, at least in the Swedish genetic form of Alzheimer's disease.

L22 ANSWER 30 OF 48 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 1997:466579 BIOSIS
DOCUMENT NUMBER: PREV199799765782
TITLE: Identification and **characterization** of a cysteine proteinase from AD brain as a candidate **beta-secretase**: Binding and degradation properties for APP.
AUTHOR(S): Abraham, C. R.; Chang, T.; Feldman, M.; Lu, R. M.; McGraw, W.
CORPORATE SOURCE: Dep. Biochem., Boston Univ. Sch. Med., Boston, MA 02218 USA
SOURCE: Society for Neuroscience Abstracts, (1997) Vol. 23, No. 1-2, pp. 5.
Meeting Info.: 27th Annual Meeting of the Society for Neuroscience, Part 1 New Orleans, Louisiana, USA October 25-30, 1997
ISSN: 0190-5295.
DOCUMENT TYPE: Conference; Abstract; Conference
LANGUAGE: English

L22 ANSWER 31 OF 48 MEDLINE DUPLICATE 20
ACCESSION NUMBER: 97094916 MEDLINE
DOCUMENT NUMBER: 97094916 PubMed ID: 8940150
TITLE: **Beta-secretase** processing of the beta-amyloid precursor protein in transgenic mice is efficient in neurons but inefficient in astrocytes.
AUTHOR: Zhao J; Paganini L; Mucke L; Gordon M; Refolo L; Carman M; Sinha S; Oltersdorf T; Lieberburg I; McConlogue L
CORPORATE SOURCE: Athena Neurosciences, Inc., South San Francisco, California 94080, USA.. amyloid!lisam@uunet.uu.net
CONTRACT NUMBER: AG11385 (NIA)
SOURCE: JOURNAL OF BIOLOGICAL CHEMISTRY, (1996 Dec 6) 271 (49) 31407-11.
Journal code: 2985121R. ISSN: 0021-9258.
PUB. COUNTRY: United States

DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199701
ENTRY DATE: Entered STN: 19970128
Last Updated on STN: 20000303
Entered Medline: 19970109

AB Alzheimer's disease is **characterized** by the extracellular deposition of beta-amyloid peptide (Abeta) in cerebral plaques and evidence is accumulating that amyloid is neurotoxic. Abeta is derived from the beta-amyloid precursor protein (APP). Proteolytic processing of APP by the enzyme, **beta-secretase**, produces the N terminus of Abeta, and releases a secreted ectodomain of APP (beta-s-APP). To develop animal models for measuring **beta-secretase** activity in specific brain cells in vivo, we have targeted the expression of the full-length human APP to either neurons or astrocytes in transgenic mice using the neuron- specific enolase (NSE) promoter or a modified glial fibrillary acidic protein (GFAP) gene, respectively. The APP cDNAs expressed were mutated (KM to NL at 670/671) to encode amino acid substitutions that enhance amyloidogenic processing in vitro. Western analyses revealed abundant production of beta-s-APP in the brains of NSE-APP mice and enzyme-linked immunosorbent assay analyses showed production of Abeta in fetal primary mixed brain cultures and brain homogenates from these transgenic animals. Because the NSE promoter drives expression primarily in neurons, this provides in vivo evidence that the **beta-secretase** cleavage necessary for generation of beta-s-APP and Abeta is efficiently performed in neurons. In contrast, only little beta-s-APP was detected in brain homogenates of GFAP-APP mice, indicating that astrocytes show very little **beta-secretase** activity in vivo. This provides strong in vivo evidence that the major source of Abeta in brain is from neurons and not from astrocytes.

L22 ANSWER 32 OF 48 MEDLINE DUPLICATE 21
ACCESSION NUMBER: 96394436 MEDLINE
DOCUMENT NUMBER: 96394436 PubMed ID: 8798542
TITLE: Enhanced amyloidogenic processing of the beta-amyloid precursor protein in gene-targeted mice bearing the Swedish familial Alzheimer's disease mutations and a "humanized" Abeta sequence.
AUTHOR: Reaume A G; Howland D S; Trusko S P; Savage M J; Lang D M; Greenberg B D; Siman R; Scott R W
CORPORATE SOURCE: Cephalon, Inc., West Chester, Pennsylvania 19380, USA.
SOURCE: JOURNAL OF BIOLOGICAL CHEMISTRY, (1996 Sep 20) 271 (38) 23380-8.
Journal code: 2985121R. ISSN: 0021-9258.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199611
ENTRY DATE: Entered STN: 19961219
Last Updated on STN: 20000303
Entered Medline: 19961119

AB The processing of the beta-amyloid precursor protein (APP) in vivo has been **characterized** in a novel animal model that recapitulates, in part, the APP genotype of a familial form of Alzheimer's disease (AD). A gene-targeting strategy was used to introduce the Swedish familial AD mutations and convert mouse Abeta to the human sequence. The mutant APP is expressed at normal levels in brain, and cleavage at the mutant **beta-secretase** site is both accurate and enhanced. Furthermore, human Abeta production is significantly increased to levels 9-fold greater than those in normal human brain while nonamyloidogenic processing is depressed. The results on Abeta production extend similar findings obtained in cell culture to the brain of an animal and substantiate Abeta as a etiological factor in Swedish familial AD. These animals provide several distinguishing features over others created by conventional transgenic methodologies. The spatial and temporal expression patterns of human Abeta are expected to be faithfully reproduced because the gene encoding the mutant APP remains in its normal chromosomal context. Thus, the neuropathological consequences of human Abeta

overproduction can be evaluated longitudinally in the absence of potential mitigating effects of APP overexpression or presence of the mouse Abeta peptide.

L22 ANSWER 33 OF 48 MEDLINE DUPLICATE 22
ACCESSION NUMBER: 96217377 MEDLINE
DOCUMENT NUMBER: 96217377 PubMed ID: 8632167
TITLE: Evaluation of cathepsins D and G and EC 3.4.24.15 as candidate **beta-secretase** proteases using peptide and amyloid precursor protein substrates.
AUTHOR: Brown A M; Tummolo D M; Spruyt M A; Jacobsen J S; Sonnenberg-Reines J
CORPORATE SOURCE: CNS Disorders, Wyeth-Ayerst Research, Princeton, New Jersey 08543, USA.
SOURCE: JOURNAL OF NEUROCHEMISTRY, (1996 Jun) 66 (6) 2436-45. Journal code: 2985190R. ISSN: 0022-3042.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199607
ENTRY DATE: Entered STN: 19960715
Last Updated on STN: 20000303
Entered Medline: 19960701

AB No single protease has emerged that possesses all the expected properties for **beta-secretase**, including brain localization, appropriate peptide cleavage specificity, and the ability to cleave amyloid precursor protein exactly at the amino-terminus of beta-amyloid peptide. We have **isolated** and **purified** a brain-derived activity that cleaves the synthetic peptide substrate SEVKMDAEF between methionine and aspartate residues, as required to generate the amino-terminus of beta-amyloid peptide. Its molecular size of 55-60 kDa and inhibitory profile indicate that we have **purified** the metalloprotease EC 3.4.24.15. We have compared the sequence specificity of EC 3.4.24.15, cathepsin D, and cathepsin G for their ability to cleave the model peptide SEVKMDAEF or related peptides that contain substitutions reported to modulate beta-amyloid peptide production. We have also tested the ability of these enzymes to form carboxyl-terminal fragments from full-length, membrane-embedded amyloid precursor protein substrate or amyloid precursor protein that contains the Swedish KM --> NL mutation. The correct cleavage was tested with an antibody specific for the free amino-terminus of beta-amyloid peptide. Our results exclude EC 3.4.24.15 as a candidate **beta-secretase**. Although cathepsin G cleaves the model peptide correctly, it displays poor ability to cleave the Swedish KM --> NL peptide and does not generate carboxy-terminal fragments that are immunoreactive with amino-terminal-specific antiserum. Cathepsin D does not cleave the model peptide or show specificity for wild-type amyloid precursor protein; however, it cleaves the Swedish "NL peptide" and "NL precursor" substrates appropriately. Our results suggest that cathepsin D could act as **beta-secretase** in the Swedish type of familial Alzheimer's disease and demonstrate the importance of using full-length substrate to verify the sequence specificity of candidate proteases.

L22 ANSWER 34 OF 48 MEDLINE DUPLICATE 23
ACCESSION NUMBER: 96373739 MEDLINE
DOCUMENT NUMBER: 96373739 PubMed ID: 8780030
TITLE: Monoclonal antibodies against the human metalloprotease EC 3.4.24.15 label neurofibrillary tangles in Alzheimer's disease brain.
AUTHOR: Conn K J; Pietropaolo M; Ju S T; Abraham C R
CORPORATE SOURCE: Department of Medicine, Boston University School of Medicine, Massachusetts 02118, USA.
CONTRACT NUMBER: AG 00001 (NIA)
AG 09905 (NIA)
SOURCE: JOURNAL OF NEUROCHEMISTRY, (1996 May) 66 (5) 2011-8. Journal code: 2985190R. ISSN: 0022-3042.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals

ENTRY MONTH: 199701
ENTRY DATE: Entered STN: 19970128
Last Updated on STN: 20000303
Entered Medline: 19970114

AB Alzheimer's disease is **characterized** neuropathologically by the presence of neuritic and amyloid plaques, vascular amyloid, and neurofibrillary tangles in specific brain areas. The main constituent of amyloid deposits is amyloid beta protein, a 40-42 amino acid proteolytic product of the amyloid beta-precursor protein. In our search for proteases that can generate the N-terminus of amyloid beta protein (**beta-secretases**), we discovered a thiol-dependent metalloprotease that was identified, by peptide sequencing, as metalloendopeptidase EC 3.4.24.15. In vitro, the metalloprotease cleaves the methionine-aspartic acid bond in a 10 amino acid synthetic peptide, indicating that it could generate the N-terminus of amyloid beta protein, and generates amyloidogenic fragments from full-length recombinant amyloid beta-precursor protein. Mouse monoclonal antibodies produced against a unique synthetic peptide from the metalloprotease labeled various monkey tissues as detected by western blots and immunohistochemistry. Unexpectedly, two monoclonal antibodies, IVD6 and IIIF3, immunolabeled strongly intracellular neurofibrillary tangles, neurites of senile plaques, and neuropil threads, but not "ghost" tangles or amyloid in sections taken from Alzheimer's disease brain. This finding provides further evidence for the metalloprotease's relevance to Alzheimer's disease pathology, although the connection between tangle staining and the formation of amyloid beta protein remains to be elucidated.

L22 ANSWER 35 OF 48 MEDLINE DUPLICATE 24
ACCESSION NUMBER: 97073150 MEDLINE
DOCUMENT NUMBER: 97073150 PubMed ID: 8915898
TITLE: Metabolites of the beta-amyloid precursor protein generated by **beta-secretase** localise to the trans-Golgi network and late endosome in 293 cells.
AUTHOR: Stephens D J; Austen B M
CORPORATE SOURCE: Department of Surgery, St. George's Hospital Medical School, London, United Kingdom.
SOURCE: JOURNAL OF NEUROSCIENCE RESEARCH, (1996 Oct 15) 46 (2) 211-25.
Journal code: 7600111. ISSN: 0360-4012.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199703
ENTRY DATE: Entered STN: 19970321
Last Updated on STN: 20000303
Entered Medline: 19970310

AB Deposition of beta-amyloid occurs in the brains of all sufferers of Alzheimer's disease. beta-amyloid is proteolytically derived from the beta-amyloid precursor protein by as yet unidentified enzymes termed secretases. We have generated and **characterised** antisera to the carboxy-terminal domain and **beta-secretase** cleavage site of the Alzheimer's amyloid precursor protein. The **beta-secretase** cleavage event occurs at the extreme N-terminus of the beta-amyloid peptide. Our antiserum to the N-terminus of the beta-amyloid peptide (NT beta 4) specifically recognises **beta-secretase** cleaved species as opposed to intact beta APP. NT beta 4 specifically immunoprecipitates a 13 kDa fragment of beta APP (p13) which is potentially amyloidogenic. We have used these antisera in confocal laser scanning immunofluorescence microscopy to localise the intracellular location of potentially amyloidogenic beta APP processing fragments such as p13. Using a number of marker antisera of known intracellular location, we have defined the major location of beta APP fragments possessing the Asp-1 N-terminus of beta-amyloid as the trans-Golgi network or late endosome on the basis of colocalisation with a monoclonal antibody to the cation-independent mannose-6-phosphate receptor. The colocalisation was further investigated using brefeldin A which demonstrated that the p13 fragment and mannose-6-phosphate receptor are trafficked by alternative pathways from the trans-Golgi network.

L22 ANSWER 36 OF 48 MEDLINE DUPLICATE 25

ACCESSION NUMBER: 96310887 MEDLINE
DOCUMENT NUMBER: 96310887 PubMed ID: 8755488
TITLE: Inhibition of amyloid beta-protein production in neural cells by the serine protease inhibitor AEBSF.
AUTHOR: Citron M; Diehl T S; Capell A; Haass C; Teplow D B; Selkoe D J
CORPORATE SOURCE: Department of Neurology, Harvard Medical School, Boston, Massachusetts 02115, USA.
CONTRACT NUMBER: AG05134 (NIA)
AG12749 (NIA)
SOURCE: NEURON, (1996 Jul) 17 (1) 171-9.
Journal code: 8809320. ISSN: 0896-6273.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199612
ENTRY DATE: Entered STN: 19970128
Last Updated on STN: 19970128
Entered Medline: 19961223

AB Cerebral deposition of amyloid beta protein (A beta) is an early and critical feature of Alzheimer's disease. A beta production requires the proteolytic release of A beta from the beta-amyloid precursor protein (beta APP). Thus, inhibition of A beta release is a prime therapeutic goal. Here, we show that the broad spectrum, irreversible serine protease inhibitor, AEBSF, inhibits the constitutive production of A beta in five different human cell lines, both neural and nonneural. AEBSF also stabilizes full-length beta APP and enhances alpha-secretion, as shown by an increase in the proteolytic derivative, alpha-APPS. Further, we demonstrate that the inhibitory effect of AEBSF is specific for A beta proteins starting at Aspartate 1, suggesting that AEBSF directly inhibits **beta-secretase**, the Methionine-Aspartate (Met-Asp)-cleaving enzyme. These results indicate that specific inhibition of this A beta-generating protease is possible in living human neural cells and provide information about the **characteristics** of this as yet unidentified enzyme.

L22 ANSWER 37 OF 48 MEDLINE DUPLICATE 26
ACCESSION NUMBER: 96187000 MEDLINE
DOCUMENT NUMBER: 96187000 PubMed ID: 8624127
TITLE: The role of APP processing and trafficking pathways in the formation of amyloid beta-protein.
AUTHOR: Selkoe D J; Yamazaki T; Citron M; Podlisny M B; Koo E H; Teplow D B; Haass C
CORPORATE SOURCE: Centre for Neurologic Diseases, Brigham and Women's Hospital, Boston, Massachusetts 02115, USA..
Selkoe@cnd.bwh.harvard.edu
CONTRACT NUMBER: AG 07911-07 (NIA)
AG06173-10 (NIA)
SOURCE: ANNALS OF THE NEW YORK ACADEMY OF SCIENCES, (1996 Jan 17) 777 57-64. Ref: 19
Journal code: 7506858. ISSN: 0077-8923.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199606
ENTRY DATE: Entered STN: 19960627
Last Updated on STN: 19960627
Entered Medline: 19960614

AB The amyloid beta-protein (A beta) is a proteolytic fragment of the beta-amyloid precursor protein (beta APP). We previously reported the constitutive secretion of A beta peptides from a variety of cells expressing beta APP under normal culture conditions. These endogenously produced A beta peptides have heterogeneous N- and C-termini that vary as a function of beta APP missense mutations. Treatment of A beta-secreting cells with agents that alter intravesicular pH showed that an acidic compartment is required for proper A beta generation. One such compartment appears to be the endosome. Immunolabeling of cell-surface beta APP in

living neurons and non-neuronal cells directly demonstrated the endocytosis of the protein and its rapid recycling (within 5-10 minutes) to the cell surface, as well as the trafficking of some beta APP to lysosomes. Expression of beta APP with various deletions of the cytoplasmic domain, including the NPTY motif, leads to decreased internalization and an associated decrease in the production of A beta peptides that begin at the usual aspl start site. These and other data suggest that A beta production begins with cleavage of beta APP by a still unknown protease(s) (**beta-secretase**[s]) at the met-asp bond proceeding the A beta N-terminus and that this occurs in part in early endosomes. To **characterize** the substrate requirements of **beta-secretase**, beta APP was mutagenized by placing stop codons within or at the end of the transmembrane domain or substituting other amino acids for the wild-type met and asp at the P1 and P1' positions. These experiments showed that proper **beta-secretase** cleavage requires the precursor to be membrane-anchored and is highly sequence specific; most substitutions at met or asp substantially decrease A beta production. Analogous mutagenesis experiments around the A beta C-terminus revealed that the unknown protease(s) cleaving here ("gamma-secretase[s]") does not show such specificity. Cells secreting A beta may also be useful for examining the critical issue of the aggregation of A beta into its neurotoxic polymeric form under physiological conditions. In this regard, we have found that beta APP-expressing CHO cells show aggregation of > or = 10-20% of their secreted A beta peptides into SDS-stable dimers, trimers and sometimes tetramers under normal culture conditions. The identity of these small multimers was confirmed by extensive immunochemical **characterization** and radiosequencing. They are present at approximately 100-500 pM levels in conditioned medium of CHO transfectants. Using this endogenous A beta aggregating system, we have begun to examine variables that influence aggregation and compounds which may retard it. In conclusion, studies of the regulation of A beta production and aggregation in cell culture can provide information under physiological conditions that can complement analyses of these processes in vivo.

L22 ANSWER 38 OF 48 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 1996:251892 BIOSIS
DOCUMENT NUMBER: PREV199698808021
TITLE: **Characterization** of **beta-secretase** cleavage of the amyloid precursor protein in human HEK-293 cells.
AUTHOR(S): Schrader-Fischer, G.; Paganetti, P. A.
CORPORATE SOURCE: Sandoz Res. Inst., CH-3001 Berne Switzerland
SOURCE: Experientia (Basel), (1996) Vol. 52, No. ABSTR., pp. A3. Meeting Info.: 28th Annual Meeting of the Swiss Societies for Experimental Biology (USGEB/USSBE) Zuerich-Irchel, Switzerland March 27-29, 1996
ISSN: 0014-4754.
DOCUMENT TYPE: Conference
LANGUAGE: English

L22 ANSWER 39 OF 48 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1995:786876 CAPLUS
DOCUMENT NUMBER: 123:224499
TITLE: The metabolism of the amyloid precursor protein and its relevance to Alzheimer's disease
AUTHOR(S): Sinha, Sukanto
CORPORATE SOURCE: Athena Neurosciences, San Francisco, CA, 94080, USA
SOURCE: Perspectives in Drug Discovery and Design (1995), 2(3), 363-9
CODEN: PDDDEC; ISSN: 0928-2866
PUBLISHER: ESCOM
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
AB A review and discussion with 41 refs. The pathol. of Alzheimer's disease is primarily **characterized** by the deposition of .beta.-amyloid/A.beta. peptide as the major component of senile or neuritic plaques. The A.beta. peptide is produced as a result of proteolytic cleavage of the transmembrane protein precursor, APP, during its normal cellular metab. The free amino terminus of the A.beta. peptide

is generated by an endopeptidic cleavage between Met671-Asp672 by a protease termed .**beta**.-**secretase**. Increased cleavage at this site takes place in a rare, inherited double mutation (Lys670-Met671 to Asn670-Leu671), leading to increased A.beta. prodn. and consequent development of Alzheimer's disease on an accelerated time scale in the affected individuals, underscoring the pathol. importance of . **beta**.-**secretase** activity. Cellular studies provide direct evidence that inhibition of .**beta**.-**secretase** activity would appear to be effective in inhibiting A.beta. prodn. as a rational approach to developing therapeutics for the disease.

L22 ANSWER 40 OF 48 MEDLINE DUPLICATE 27
ACCESSION NUMBER: 96122180 MEDLINE
DOCUMENT NUMBER: 96122180 PubMed ID: 8537184
TITLE: Brain cathepsin B but not metalloendopeptidases degrade rAPP751 with production of amyloidogenic fragments. Comparison with synthetic peptides emulating beta- and gamma-secretase sites.
AUTHOR: Marks N; Berg M J; Sapirstein V S; Durrie R; Swistok J; Makofske R C; Danho W
CORPORATE SOURCE: Department of Neurochemistry, Nathan Kline Institute for Psychiatric Research, Orangeburg, New York, USA.
SOURCE: INTERNATIONAL JOURNAL OF PEPTIDE AND PROTEIN RESEARCH, (1995 Sep-Oct) 46 (3-4) 306-13.
Journal code: 0330420. ISSN: 0367-8377.
PUB. COUNTRY: Denmark
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199602
ENTRY DATE: Entered STN: 19960221
Last Updated on STN: 20020420
Entered Medline: 19960208

AB Lysosomal cathepsin B but not L degraded rAPP751 to yield C-terminal 19-25 kDa fragments containing beta A4, reinforcing the view that acidic proteases participate in endosomal-lysosomal processing to yield amyloidogenic fragments in situ. This mechanism is consistent with fragmentation of endogenous APPs within clathrin-coated vesicles (CVs) by vesicular hydrolases, with the appearance of C-terminal amyloidogenic fragments following incubation at pH 6.5. A neutral endopeptidase resembling NEP 24.11 (PS-NEP) **purified** from detergent extracts of human brain degraded rAPP751; however, breakdown was not blocked robustly by metal chelators or phosphoramidon, suggesting the presence of an alternative processing enzyme. Effects of other inhibitors showed that breakdown was mediated by serine-protease-like component(s). A phosphoramidon-insensitive metalloendopeptidase (PI-NEP) partially **purified** from rat brain P2 using detergents, and resembling NEP 24.15, showed no activity towards rAPP751. Peptides containing putative beta- or gamma-secretase sites were synthesized for purposes of examining their metabolism by the brain enzymes. Those containing **beta-secretase** sites were hydrolysed at one or more sites by the four enzymes, but only PI- and PS-NEP acted at the Met-Asp site of Ac-Val-Lys-Met-Asp-Ala-Glu-Phe-Arg.NH2. In the case of substrates containing the gamma-site, these two categories of enzymes were the only ones degrading N-Ac-Ile-Ala.NH2. These data imply that the brain metalloendopeptidases, while inactive towards intact precursors, may be involved in turnover of intermediates containing beta- or gamma-sites.

L22 ANSWER 41 OF 48 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 95270243 EMBASE
DOCUMENT NUMBER: 1995270243
TITLE: Amyloid beta amyloidosis in Alzheimer's disease.
AUTHOR: Price D.L.; Sisodia S.S.; Gandy S.E.
CORPORATE SOURCE: Neuropathology Laboratory, Johns Hopkins University, School of Medicine, 730 Rutland Avenue,Baltimore, MD 21205, United States
SOURCE: Current Opinion in Neurology, (1995) 8/4 (268-274).
ISSN: 1350-7540 CODEN: CONEEX
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 005 General Pathology and Pathological Anatomy

008 Neurology and Neurosurgery
029 Clinical Biochemistry
LANGUAGE: English
SUMMARY LANGUAGE: English
AB The presence of amyloid deposits in the parenchyma of the amygdala, hippocampus, and neocortex Is a major histopathological hallmark of Alzheimer's disease. The principal component of amyloid is amyloid beta, a 39-43 amino acid peptide comprised of a portion of the transmembrane domain and the extracellular domain of the amyloid precursor proteins. Amyloid precursor proteins occur as several amyloid beta-containing isoforms of 695, 751, and 770 amino acids. In cultured cells, amyloid precursor proteins mature through the constitutive secretory pathway, and some cell-surface-bound amyloid precursor proteins are cleaved by an enzyme, designated as alpha-secretase, within the amyloid beta domain, an event that precludes amyloid beta amyloidogenesis. Two additional pathways of amyloid precursor protein processing include an endosomal/lysosomal pathway that generates a complex set of amyloid precursor protein-related membrane-bound fragments, some of which contain the entire amyloid beta sequence; and, by mechanisms not fully understood, secretion of amyloid beta 1-40 into the conditioned medium in vitro and its presence in cerebrospinal fluid in vivo. The intracellular sites of enzymes responsible for proteolytic cleavage at the amino- and carboxyl-termini of amyloid beta, termed gamma- and **beta-secretase**, respectively, have not been identified. Molecular genetic investigations have identified a variety of mutations in the amyloid precursor protein gene that segregate with early-onset familial Alzheimer's disease and with hereditary cerebral hemorrhage with amyloid, Dutch type. Several of these mutations appear to influence amyloid precursor protein processing and result in the production of higher levels or longer amyloid beta-related peptides that are inherently more fibrillogenic. Although a variety of lines of evidence implicate amyloid precursor protein and amyloid beta in Alzheimer's disease, the mechanism(s) by which amyloid beta influences the biology and vulnerability of neural cells is not fully clear. Amyloid beta toxicity is being explored in vitro and in vivo. Finally, recent progress has been made in the generation of transgenic mice expressing amyloid precursor protein or amyloid beta that recapitulate a subset of the pathology observed in Alzheimer's disease.

L22 ANSWER 42 OF 48 MEDLINE
ACCESSION NUMBER: 1998005196 MEDLINE
DOCUMENT NUMBER: 98005196 PubMed ID: 9346839
TITLE: Cleavage of a beta-amyloid precursor sequence by cathepsin D.
AUTHOR: Austen B M; Stephens D J
CORPORATE SOURCE: Department of Surgery, St George's Hospital Medical School, London, England, U.K.
SOURCE: BIOMEDICAL PEPTIDES, PROTEINS AND NUCLEIC ACIDS, (1995) 1 (4) 243-6.
Journal code: 9506699. ISSN: 1353-8616.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199711
ENTRY DATE: Entered STN: 19971224
Last Updated on STN: 19971224
Entered Medline: 19971114
AB The identify of the proteases that release beta-amyloid, found in the senile plaques of Alzheimer's disease, from its precursor APP, have not been rigorously identified. As senile plaques contain lysosomal enzymes, and production of some of the amyloidogenic intermediates are inhibited by lysosomotrophic agents, it has been suggested that cathepsins are involved in amyloidogenesis. A synthetic 31-residue peptide overlapping the **beta-secretase** cleavage site is found to be digested at two mutually exclusive sites, one and three residues on the N-terminal side of the N-terminal Asp residue of beta-amyloid. Coupled with the action of aminopeptidases, lysosomal or endosomal cathepsin D could be responsible for generating the N-terminus of beta-amyloid in vivo.

L22 ANSWER 43 OF 48 SCISEARCH COPYRIGHT 2003 ISI (R)
ACCESSION NUMBER: 95:344627 SCISEARCH

THE GENUINE ARTICLE: QT865
TITLE: DETECTION AND **CHARACTERIZATION** OF **BETA -SECRETASE** CLEAVED APP FROM CELL-LINES
AUTHOR: GRAY C W (Reprint); CHRISTIE G; OWEN D E; WATT I; CHAMBERLAIN P; HOLMES D; ALLSOP D; ROBERTS G W
CORPORATE SOURCE: SMITHKLINE BEECHAM PHARMACEUT, MOLEC NEUROPATHOL RES, HARLOW CM19 5AW, ESSEX, ENGLAND
COUNTRY OF AUTHOR: ENGLAND
SOURCE: JOURNAL OF CELLULAR BIOCHEMISTRY, (02 APR 1995) Supp. 21B, pp. 103.
ISSN: 0730-2312.
DOCUMENT TYPE: Conference; Journal
FILE SEGMENT: LIFE
LANGUAGE: ENGLISH
REFERENCE COUNT: No References

L22 ANSWER 44 OF 48 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 1995:278214 BIOSIS
DOCUMENT NUMBER: PREV199598292514
TITLE: Detection and **characterisation** of **beta-secretase** cleaved APP from cell lines.
AUTHOR(S): Gray, C. W.; Christie, G.; Owen, D. E.; Watt, I.; Chamberlain, P.; Holmes, S.; Allsop, D.; Roberts, G. W.
CORPORATE SOURCE: Mol. Neuropathol. Res., SmithKline Beecham Pharm., Harlow, Essex CM19 5AW UK
SOURCE: Journal of Cellular Biochemistry Supplement, (1995) Vol. 0, No. 21B, pp. 103.
Meeting Info.: Keystone Symposium on the Molecular and Cellular Basis of Human Neurodegenerative Disease Breckenridge, Colorado, USA April 3-9, 1995
ISSN: 0733-1959.
DOCUMENT TYPE: Conference
LANGUAGE: English

L22 ANSWER 45 OF 48 MEDLINE DUPLICATE 28
ACCESSION NUMBER: 94292541 MEDLINE
DOCUMENT NUMBER: 94292541 PubMed ID: 8021287
TITLE: Mutations associated with a locus for familial Alzheimer's disease result in alternative processing of amyloid beta-protein precursor.
AUTHOR: Haass C; Hung A Y; Selkoe D J; Teplow D B
CORPORATE SOURCE: Department of Neurology, Harvard Medical School, Boston, Massachusetts 02115.
CONTRACT NUMBER: AG06173-09 (NIA)
AG07911-06 (NIA)
SOURCE: JOURNAL OF BIOLOGICAL CHEMISTRY, (1994 Jul 1) 269 (26) 17741-8.
Journal code: 2985121R. ISSN: 0021-9258.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199407
ENTRY DATE: Entered STN: 19940815
Last Updated on STN: 19980206
Entered Medline: 19940729

AB Alzheimer's disease (AD) is a progressive neurodegenerative disorder **characterized** by the extracellular deposition of amyloid beta-protein (A beta), a molecule produced by post-translational processing of the beta-amyloid precursor protein (beta APP). Mutations within the gene encoding beta APP have been linked to early onset forms of AD, but the pathogenetic mechanism(s) producing the phenotype are unknown. We analyzed the effects on beta APP processing in vitro of a naturally occurring Ala-->Gly mutation at position 692 of beta APP770 (A692G) (Hendriks, L., Duijin, C., Cras, P., Cruts, M., van Hul, W., van Harskamp, F., Warren, A., McInnis, M., Antonarakis, S., Martin, J.-J., Hofman, A., and van Broeckhoven, C. (1992) Nature Genet. 1, 218-221), as well as the effects of five genetically engineered mutations at or near this site. Substitution of glycine or proline for Ala692, or for Phe690, produced relative increases in secretion of A beta and relative decreases in secretion of the p3 peptide(s) arising after alpha-secretase generation of

soluble APP (APPs). The Phe690-->Pro substitution also resulted in the synthesis of truncated APPs molecules. The structurally conservative substitutions Ala692-->Val and Phe690-->Tyr did not exhibit these effects. Certain of the substitutions also resulted in the production of a minor peptides, previously undescribed in vitro, beginning at Ala2, Lys16, and Phe19 of A beta. These data show that beta APP mutations carboxyl-terminal to alpha-secretase and **beta-secretase** cleavage sites can exert strong control over beta APP processing. Increased secretion of A beta may accelerate amyloidogenesis by providing more precursors for aggregation. It is also possible that truncated A beta peptides resulting from several of these mutations may accelerate amyloidogenesis through self-aggregation and/or seeding the fibrillogenesis of longer, more abundant A beta species.

L22 ANSWER 46 OF 48 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 1994:420524 BIOSIS
DOCUMENT NUMBER: PREV199497433524
TITLE: **Purification** and **characterization** of forms of s-beta-PP specifically cleaved at alpha-secretase or **beta-secretase** sites.
AUTHOR(S): Murphy, M. F.; Rowe, B. A.; Vasserman, E. D.; Axelrod, F. T.; Albrecht, E.; Wagner, S. L.; Siegel, R. S.
CORPORATE SOURCE: SIBIA, La Jolla, CA 92037 USA
SOURCE: Neurobiology of Aging, (1994) Vol. 15, No. SUPPL. 1, pp. S634-S64.
Meeting Info.: Fourth International Conference on Alzheimer's Disease and Related Disorders Minneapolis, Minnesota, USA July 29-August 3, 1994
ISSN: 0197-4580.
DOCUMENT TYPE: Conference
LANGUAGE: English

L22 ANSWER 47 OF 48 MEDLINE DUPLICATE 29
ACCESSION NUMBER: 94286413 MEDLINE
DOCUMENT NUMBER: 94286413 PubMed ID: 8015976
TITLE: Hydrolysis of amyloid precursor protein-derived peptides by cysteine proteinases and extracts of rat brain clathrin-coated vesicles.
AUTHOR: Marks N; Berg M J; Chi L M; Choi J; Durrie R; Swistok J; Makofske R C; Danho W; Sapirstein V S
CORPORATE SOURCE: Division of Neurochemistry, Nathan Kline Institute for Psychiatric Research, Orangeburg, NY 10962.
SOURCE: PEPTIDES, (1994 Jan) 15 (1) 175-82.
Journal code: 8008690. ISSN: 0196-9781.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199407
ENTRY DATE: Entered STN: 19940810
Last Updated on STN: 20020420
Entered Medline: 19940726

AB Amyloid precursor proteins (APPs) and C-terminal fragments were colocalized with cysteine proteinase-like enzymes in **purified** rat brain clathrin-coated vesicles. Vesicular extracts degraded beta A4(12-28), yielding a product profile similar to that of **purified** rat brain cathepsin B. Cathepsin B degraded this peptide sequentially, with initial cleavage occurring at Val18-Phe19 and Phe19-Phe20 followed by release of dipeptides. Enzyme also hydrolyzed beta A4(1-40) at Phe19-Phe20 bond but at lower rates, likely due to aggregate formation. An octapeptide analogue of the domain adjacent to beta A4 (N-Ac-Val-Lys-Met-Asp-Ala-Glu-Phe-NH2) was also hydrolyzed by brain cathepsins B and L, and metalloendopeptidase 24.11. Enzymes acted at multiple sites, but only 24.11 cleaved the Met-Asp bond, thus resembling a proposed **beta-secretase**. Data imply that clathrin-coated vesicles contain cysteine-like proteinases capable of initiating the processing of APP or its fragments.

L22 ANSWER 48 OF 48 SCISEARCH COPYRIGHT 2003 ISI (R)
ACCESSION NUMBER: 94:441179 SCISEARCH
THE GENUINE ARTICLE: NV609

TITLE: **PURIFICATION** AND **CHARACTERIZATION** OF FORMS OF S-BETA-PP SPECIFICALLY CLEAVED AT ALPHA-SECRETASE OR **BETA-SECRETASE** SITES

AUTHOR: MURPHY M F (Reprint); ROWE B A; VASSERMAN E D; AXELROD F T; ALBRECHT E; WAGNER S L; SIEGEL R S

CORPORATE SOURCE: SIBIA, LA JOLLA, CA, 92037

COUNTRY OF AUTHOR: USA

SOURCE: NEUROBIOLOGY OF AGING, (1994) Vol. 15, Supp. 1, pp. S63-S64.
ISSN: 0197-4580.

DOCUMENT TYPE: Conference; Journal

FILE SEGMENT: LIFE

LANGUAGE: ENGLISH

REFERENCE COUNT: No References

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Access DB# _____

SEARCH REQUEST FORM

Scientific and Technical Information Center

Requester's Full Name: M. A. WALICKA Examiner #: 78201 Date: Apr. 22,
Art Unit: 1652 Phone Number 305-7270 Serial Number: 09/723,722
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10D01

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Please provide a detailed statement of the search topic, and describe as specifically as possible the subject matter to be searched. Include the elected species or structures, keywords, synonyms, acronyms, and registry numbers, and combine with the concept or utility of the invention. Define any terms that may have a special meaning. Give examples or relevant citations, authors, etc. if known. Please attach a copy of the cover sheet, pertinent claims, and abstract.

Title of Invention: Beta - secretase enzymes compositions &

Inventors (please provide full names): Anderson J. et al.

Earliest Priority Filing Date: 06/15/1999

**For Sequence Searches Only* Please include all pertinent information (parent, child, divisional, or issued patent numbers) along with the appropriate serial number.*

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